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Vol. 41 NOVEMBER, 1952 No. 5

# THE JOURNAL OF PEDIATRICS

A MONTHLY JOURNAL DEVOTED TO THE PROBLEMS AND DISEASES OF INFANCY AND CHILDHOOD

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Vol. 41, No. 5, November, 1952. The Journal of Pediatrics is published monthly by The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, Mo. Subscription price: The United States, its Possessions and Pan-American Countries, $12.00 a year; Canada and other foreign countries, $13.00 a year. Entered as Second-class matter June 29, 1932, at the Post Office at St. Louis, Missouri, under the Act of March 3, 1879. Printed in the U. S. A.

The Journal of Pediatrics

VOL. 41 NOVEMBER, 1952 No. 5

# THE NEPHROTIC SYNDROME IN CHILDREN

## I. CLINICAL RESPONSE TO NITROGEN MUSTARD THERAPY

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THE etiology of the nephrotic syndrome remains obscure, despite extensive investigation and speculation over a period of many years. There is disagreement among investigators as to whether this syndrome always represents a phase of glomerulonephritis or may represent a distinct and separate entity.[1] Recently, the concept of its pathogenesis being based on an abnormal immune response has gained favor.[2, 3] This concept is given implicit support by animal experimental work which suggests that nephrotoxic nephritis in animals[4, 5, 6] results from an antigen-antibody reaction and that in certain strains of rats this experimentally produced disease may closely simulate the nephrotic syndrome as it occurs in children.[7]

Nitrogen mustard was first employed in therapy of glomerulonephritis by Chasis and associates[8, 9] in the hope that its depressant effect on the reticuloendothelial system might interfere with the antigen-antibody mechanism postulated to be involved etiologically in this syndrome. In their experience diuresis frequently resulted from this treatment. Taylor and coworkers[10] extended this work to a series of patients with the nephrotic syndrome and reported encouraging results. Nitrogen mustard inhibits antibody production[11, 12] and prevents the development of renal lesions in rabbits given an intravenous injection of a single large dose of bovine serum gamma globulin.[12] Attempts at prevention and treatment of nephrotoxic nephritis in rats with nitrogen mustard[13] met with only limited success; the animals were not completely protected against the disease, but certain manifestations of the disease, including edema, appeared to be modified.

The present report is concerned with studies of the effects, clinical and chemical, of nitrogen mustard therapy in children with the nephrotic syndrome.

### MATERIALS AND METHODS

The patients included in this study are nine children with the nephrotic syndrome. Six of these children, ranging in age from 18 months to 9 years, were suffering with lipoid nephrosis, so designated on the basis of their clinical manifestations of anasarca, ascites, albuminuria, hypoproteinemia, and hyperlipidemia without hypertension or hematuria; two children, 2 and 11 years of age, with the nephrotic syndrome secondary to a preceding typical glomerulonephritis; and one child, 14 months of age, with

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the nephrotic syndrome apparently occurring as a manifestation of Tridione toxicity. These children were observed in the pediatric departments of the Universities of Utah and Texas during the past several months. All of them have received at least one course of nitrogen mustard therapy and four have received two courses of such therapy.

Nitrogen mustard ($HN_2$) in 5 per cent dextrose in water was administered by intravenous infusion, a single course of therapy consisting of a dose of 0.2 mg. per kilogram of body weight on each of two successive days. In most cases analgesic medication was given the patient one-half hour before the administration of the nitrogen mustard.

Careful clinical and laboratory evaluation of the patients was performed at frequent intervals before and after therapy. The usual clinical laboratory determinations were done by standard methods.

## OBSERVATIONS

During the pretherapy period the nine patients suffering with the nephrotic syndrome all exhibited typical clinical evidences of their illness. The responses of various manifestations of the syndrome to therapy were quite variable and can best be understood by scrutinizing the data of individual patients.

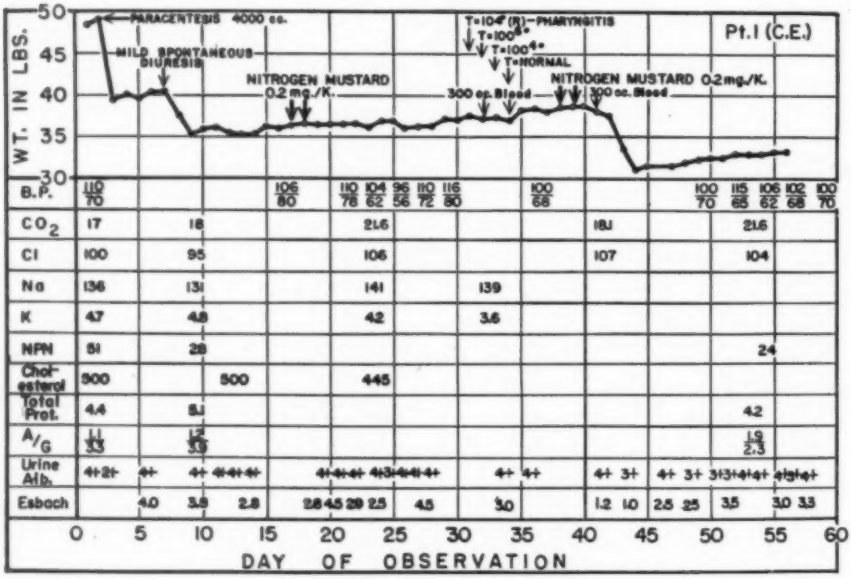


Fig. 1.—Response of Patient 1 (C. E.) to nitrogen mustard therapy.

CASE 1.—C. E., 2-year-old female. Lipoid nephrosis. Nitrogen mustard administered during third hospitalization. First course ineffective; second course effective (see Fig. 1).

The third hospital admission was on Sept. 15, 1951. The patient had marked anasarca, albuminuria, hypoproteinemia (total serum proteins = 4.4 grams per 100 c.c. and A/G ratio

= 1.1/3.3), hypercholesterolemia (500 mg. per cent), and no hematuria or hypertension. Abdominal paracentesis on the second hospital day with the removal of 4,000 c.c. of fluid resulted in a weight loss of nearly 10 pounds. Five days later a mild spontaneous diuresis occurred with loss of approximately another 5 pounds of weight, which she then slowly reaccumulated. A course of nitrogen mustard was administered on the seventeenth and eighteenth days of hospitalization with no apparent effect on the edema. However, the child's abnormal electrolyte pattern reverted toward normal following this therapy. On the thirty-eighth and thirty-ninth days of hospitalization a second course of nitrogen mustard therapy was given. On the fourth day after the initiation of this course of therapy a diuresis was initiated which resulted in a weight loss of 8 pounds during the next two days. However, she had been given a transfusion of 300 c.c. of whole blood on the forty-first day of hospitalization. Thus it is not entirely clear that the diuresis was attributable to nitrogen mustard, although it occurred at approximately the expected interval after the administration of the drug. Following this diuresis, the child continued with very little weight gain until discharge from the hospital and has continued to the present time with little change in status. It is interesting to note that at onset of diuresis following the second course of nitrogen mustard therapy the urinary protein excretion decreased quite noticeably and remained depressed for a period of approximately ten days, then returned to the original level.

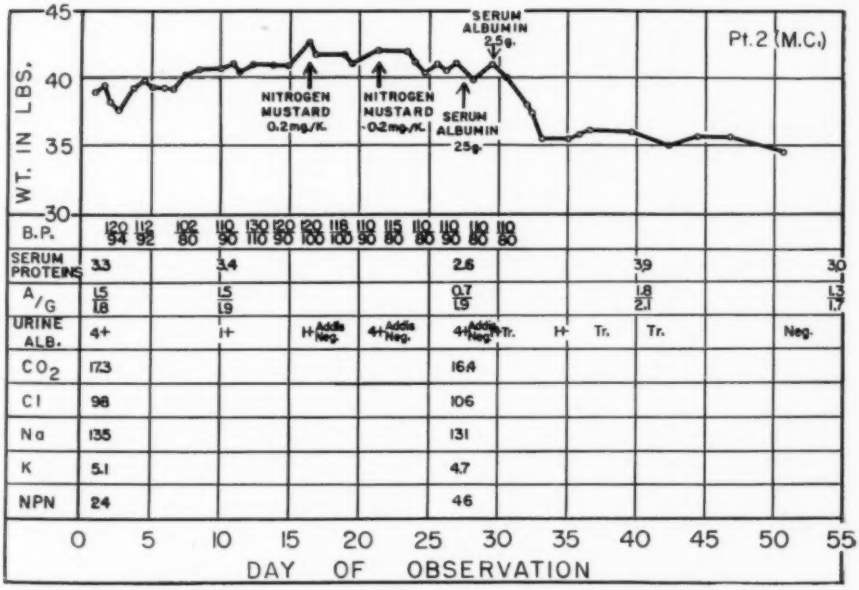


Fig. 2.—Response of Patient 2 (M. C.) to nitrogen mustard therapy.

CASE 2.—M. C., 5-year-old female. Nephrotic phase, chronic glomerulonephritis. Nitrogen mustard administered during second admission with no effect until serum albumin given (see Fig. 2).

She was first admitted to the hospital on Aug. 26, 1951. At this time she

had suffered the onset of a typical episode of acute glomerulonephritis eleven days before admission which had gradually worsened, until at the time of admission she had hypertension, marked oliguria, generalized edema, and cardiac failure. Over a seven- to ten-day period on therapy she showed marked improvement. However, she did not completely attain a base-line level before going on to the nephrotic phase of the disease with anasarca, hypoproteinemia, and massive albuminuria. A spontaneous diuresis began on September 19 and steady improvement occurred until discharge on Oct. 3, 1951. Her maximum weight had been 48½ pounds and at the time of discharge her weight was 35 pounds.

The second admission was Oct. 14, 1951. On October 10 she developed an upper respiratory infection with cough and fever, and on October 12 reaccumulation of edema began. Admission weight was 39 pounds. Nitrogen mustard therapy was initiated on the twentieth day of this hospitalization. In response to the first injection of the drug she developed fever, kidney pain, and vomiting; therefore the second injection was postponed for five days. In the meantime it was determined that no adverse hematologic effect had resulted from the initial injection. Nitrogen mustard therapy did not bring about prompt diuresis. It did, however, reduce proteinuria markedly, and when serum albumin was given on the fourteenth and sixteenth days after the initiation of therapy, a prompt diuresis occurred. It was felt that this diuresis represents an example of what might be called a "tandem" action of nitrogen mustard and serum albumin. A similar phenomenon has been observed in patients with the nephrotic syndrome treated with cortisone.[14] Until the present time she has had no further recurrence of symptoms.

CASE 3.—M. W., 9-year-old male. Lipoid nephrosis. Satisfactory response to nitrogen mustard on two occasions (see Fig. 3, *a*).

Three weeks previous to admission he had noted suborbital swelling, then swelling of the abdomen and of the ankles. Weight upon admission was 79 pounds. Nitrogen mustard was administered on the sixth and seventh days of hospitalization; diuresis began on the fifth day after initiation of this therapy and during the next several days periods of loss and reaccumulation of weight alternated but the weight finally stabilized at 61 to 63 pounds and remained in that range. The pendulum-like variations in weight initiated by nitrogen mustard in this case are of special interest. The patient remained nearly edema-free and symptom-free. However, twenty-three months later there occurred a second episode nearly identical with the first. He was again treated with nitrogen mustard with good response, and has now been edema-free and symptom-free for approximately one month.

CASE 4.—R. F.; 3-year-old male. Lipoid nephrosis. Response to nitrogen mustard temporary. Good response to ACTH therapy. (See Fig. 3, *b*.)

He was admitted to the hospital on Oct. 13, 1951, with a history of having had a rapid gain in weight, without preceding signs or symptoms of acute glomerulonephritis, starting about October 1. After twenty-five days of hospitalization, during which time his weight and symptomatology remained approximately constant, he was given a course of nitrogen mustard therapy which was followed by a diuresis starting on the second day. The minimum weight was reached on the eighth day after the initiation of therapy. Starting on the ninth day the child began to regain weight. By twenty-seven days after initiation of nitrogen mustard therapy the weight had nearly reached the pretreatment level. However, clinically he did not appear to be in as much distress as previously; and he was discharged from the hospital. He was readmitted on Jan. 5, 1952, at a weight of 41¾ pounds, rep-

resenting a weight gain of 10 pounds since his discharge one month previously. On the seventh day of this admission, therapy with ACTH was initiated with 25 I.U. q.6.h. After 4 days' administration of this dose, the dose was tapered, and finally discontinued on the twenty-third day of administration. This therapy resulted in a massive diuresis with a weight loss of 15 pounds.

CASE 5.—V. R., 3-year-old male. Lipoid nephrosis. Satisfactory response to nitrogen mustard therapy (see Fig. 3, *c*).

riod of the next week lost a total of 11 pounds. He was discharged from the hospital after twenty-seven days of hospitalization at a weight of 37 pounds. In the nineteen months that have elapsed since this patient's discharge from the hospital he has had no recurrence of symptoms of the nephrotic syndrome.

CASE 6.—K. J., 4-year-old male. Lipoid nephrosis. Satisfactory response to nitrogen mustard therapy (see Fig. 3, *d*).

This patient was admitted to the hospital on April 10, 1951. He had

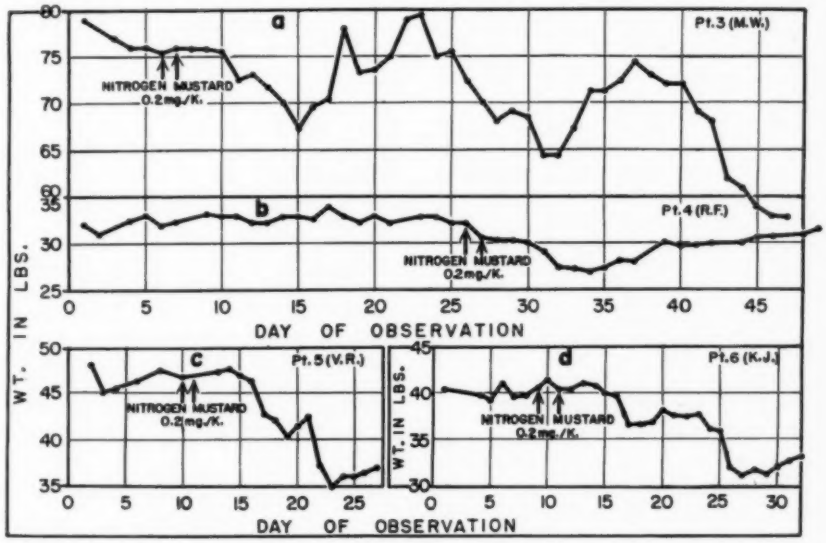


Fig. 3.—Weight response to nitrogen mustard therapy.

On July 8, 1950, this patient suddenly developed generalized edema. Previous to this, for approximately two to three months he had had periorbital edema for a short time each morning, which gradually receded during the day. He was admitted to the hospital on Oct. 18, 1950, at a weight of 48 pounds. Nitrogen mustard therapy was initiated on October 27, the tenth day of hospitalization. Six days after the first dose of nitrogen mustard, the child began to have an effective diuresis, and over the period of the next week lost a total of 11 pounds. He was discharged from the hospital after twenty-seven days of hospitalization at a weight of 37 pounds. In the nineteen months that have elapsed since this patient's discharge from the hospital he has had no recurrence of symptoms of the nephrotic syndrome.

CASE 6.—K. J., 4-year-old male. Lipoid nephrosis. Satisfactory response to nitrogen mustard therapy (see Fig. 3, *d*).

This patient was admitted to the hospital on April 10, 1951. He had become ill for the first time approximately two weeks before admission. The onset of his illness was insidious with no symptomatology of acute glomerulonephritis. Weight at the time of his admission was 40½ pounds. Nitrogen mustard therapy was initiated on the ninth day of hospitalization. Diuresis and a gradual loss in weight occurred starting on the thirteenth day, four days after the initiation of therapy. On the eighteenth day after initiation of therapy, the minimum weight of 31 pounds repre-

senting a weight loss of 9½ pounds was attained. This patient has been nearly edema-free for the past fourteen months since his discharge from the hospital.

CASE 7.—M. S., 12-year-old female. Nephrotic phase, glomerulonephritis. Temporary response to nitrogen mustard therapy.

At the time of admission she had consistent microscopic hematuria, numerous white cells, and occasional granular casts in her urine, as well as albuminuria. On the twentieth day of hospitalization, nitrogen mustard therapy was instituted. This resulted in a moderate diuresis with weight loss to 89 pounds, her admission weight having been 102 pounds and her weight at the time of initiation of therapy having been 96 pounds. However, on the twentieth day after initiation of therapy, she began to reaccumulate edema, and soon had regained her pretherapy weight. In this case, the patient's subjective improvement following nitrogen mustard therapy was quite remarkable. Her appetite improved; her attitude changed completely, and she became cheerful; there also was a disappearance from the urine of casts and all cellular elements. However, there was no definite change in the amount of albuminuria.

CASE 8.—D. L., 18-month-old male. Lipoid nephrosis. Two courses of nitrogen mustard therapy with unsatisfactory response.

This child had been well until ten days prior to admission on Oct. 11, 1951. The onset of illness was with vomiting, anorexia, and periorbital edema, followed by generalized anasarca and ascites. The first course of nitrogen mustard therapy was initiated on October 14 at which time his weight was 28¼ pounds. Diuresis commenced on the fifth day and resulted in a weight loss of 4 pounds rendering the child edema-free. However, by October 31 the patient had exceeded his pretherapy weight. A second course of nitrogen mustard was administered, starting on November 1. No diuresis occurred in response to this course of therapy. During the four months which have elapsed since this time the patient has remained edematous and symptomatic. Abdominal paracentesis has been deemed necessary for the patient's comfort on three occasions during this time.

CASE 9.—D. S., 14-month-old male. Nephrotic syndrome, presumed to be due to Tridione toxicity. No response to two courses of nitrogen mustard.

This patient developed ascites, anasarca, oliguria, hypoproteinemia, and proteinuria without hypertension or hematuria ten days previous to his admission on March 16, 1952. A course of nitrogen mustard given on the third and fourth hospital days and a second course given on the fourteenth and fifteenth days failed to produce a diuretic response. Salt-free human albumin given on the nineteenth and again on the twenty-fifth hospital day likewise failed to produce diuresis. A course of ACTH therapy consisting of 100 mg. per day for seven days was initiated on the twenty-ninth day of hospitalization and also failed to produce a diuretic response. The patient was discharged from the hospital on April 29, 1952, and until the present time has continued without improvement.

*Clinical Response to Nitrogen Mustard Therapy.*—In Table I are summarized the results with regard to production of diuresis by thirteen courses of nitrogen mustard therapy administered to nine patients suffering with the nephrotic syndrome. In four instances no diuresis occurred following the administration of nitrogen mustard while in nine instances diuresis did result. Patient 1 did not respond by diuresis to the first course of nitrogen mustard therapy. However, a second course of therapy administered three weeks later was followed by diuresis. The patient lost 8 pounds in

TABLE I. WEIGHT RESPONSE OF PATIENTS WITH THE NEPHROTIC SYNDROME TO NITROGEN MUSTARD THERAPY

| PATIENT | AGE | SEX | DURATION OF SYMPTOMS | INITIAL WEIGHT IN POUNDS | TIME IN DAYS AFTER $HN_2$ BEFORE WEIGHT LOSS | TOTAL WEIGHT LOSS IN POUNDS | TIME IN DAYS UNTIL REGAIN OF LOST WEIGHT | COMMENTS |
|---|---|---|---|---|---|---|---|---|
| 1 (C. E.) | 2 yr. | F | 17 mo. | 36 | - | 0 | - | No response. |
| | | | + 3 wk. | 39 | 4 | 8 | - | Has not regained weight. |
| 2 (M. C.) | 5 yr. | F | 2½ mo. | 42 | 15 | 7 | - | Did not respond to $HN_2$ until serum albumin given in addition. Has not regained weight. |
| 3 (M. W.) | 9 yr. | M | 1 mo. | 76 | 5 | 18 | 23 mo. | Pendulum-like weight fluctuations initially. Adequate diuresis. Edema-free for 23 months before edema recurred. |
| | | | 1 mo. | 94.5 | 3 | 27 | - | Good response. |
| 4 (R. F.) | 3 yr. | M | 1½ mo. | 32.5 | 1 | 5.5 | 26 | Weight fluctuated considerably but he had approximately regained his pretherapy weight in 26 days. |
| 5 (V. R.) | 3 yr. | M | 6 mo. | 47 | 6 | 12 | - | Has continued edema-free until the present time, 16 months later. |
| 6 (K. J.) | 4 yr. | M | 1 mo. | 41 | 4 | 10 | - | Has continued edema-free until the present time, 10 months later. |
| 7 (M. S.) | 12 yr. | F | 3 mo. | 96 | 8 | 7 | 22 | Moderate diuresis followed the administration of $HN_2$ but the edema fluid rapidly reaccumulated. |
| 8 (D.L.) | 18 mo. | M | 2 wk. | 28.5 | 5 | 4 | 17 | Satisfactory diuresis resulted from $HN_2$ but there occurred almost immediate reaccumulation of fluid. |
| | | | + 2 wk. | 32 | - | 0 | - | No response. |
| 9 (D. S.) | 14 mo. | M | 2 wk. | 23 | - | 0 | - | No response. |
| | | | + 2 wk. | 23 | - | 0 | - | No response. |

weight and has not reaccumulated edema fluid in the eight months that have elapsed since that time. Patient 8 had a satisfactory diuresis in response to his first course of nitrogen mustard therapy. However, he rapidly reaccumulated edema fluid and within seventeen days after this therapy was initiated he had regained and exceeded his pretherapy weight. A second course of nitrogen mustard therapy administered at this time failed to produce diuresis. Patient 9 failed to respond to either of two courses of nitrogen mustard therapy which were administered.

In those patients who did respond by diuresis to nitrogen mustard therapy, the diuresis did not begin immediately following the administration of the drug. The elapsed time between initiation of nitrogen mustard therapy and the onset of diuresis in these cases ranged from one to eight days. The mean elapsed time was five days. In one instance diuresis did not occur after nitrogen mustard therapy until serum albumin was administered, at which time an immediate diuresis occurred. In this case the elapsed time from initiation of nitrogen mustard therapy to onset of diuresis was fifteen days.

Of the eight individuals in this series of patients who exhibited satisfactory diuretic responses following nitrogen mustard therapy four have not regained their edema. Three of these patients reattained their pretherapy weights in seventeen, twenty-two, and twenty-six days, respectively, after the initiation of therapy; another remained nearly edema-free for twenty-three months but then suffered a second severe nephrotic episode. Since retreatment with nitrogen mustard he has not reaccumulated fluid.

Patient 7, who was suffering with the nephrotic phase of glomerulonephritis, had a short-lived weight loss in response to nitrogen mustard therapy. However, her clinical response to therapy was much better than might be assumed from consideration of weight response alone. The improvement in this child's mental attitude and general state of well-being in response to nitrogen mustard was striking. Even after reaccumulation of edema fluid this improvement persisted.

### RESPONSE OF URINARY AND SERUM PROTEINS TO NITROGEN MUSTARD THERAPY

In general, there has been no consistent decrease in proteinuria in this series of patients in response to nitrogen mustard therapy. However, Patients 2 and 6 provided notable exceptions to this generalization. Patient 2 had exhibited 4+ albuminuria during the pretherapy period and until the seventh day after initiation of nitrogen mustard therapy. However, from the ninth day after initiation of therapy the urinary albumin was never more than 1+ and by the thirty-second day had become zero. Despite this remarkable effect on urinary protein excretion, this patient did not respond by diuresis to nitrogen mustard therapy until this therapy was supplemented by the administration of serum albumin on the fourteen and sixteen days after the first administration of the drug. On the sixteenth day an effective diuresis was initiated. The patient proceeded to become edema-free and has remained so for seven months.

The effects of nitrogen mustard administration on the urinary protein excretion of Patient 6 are illustrated in Fig. 4. Likewise shown in this figure are the weight curve and daily urinary output. The correlations illustrated here among these three variables are of interest and correspond well with the idealized concept of the expected response to therapy. Unfortunately, this does not represent the usual course of events. In none of the

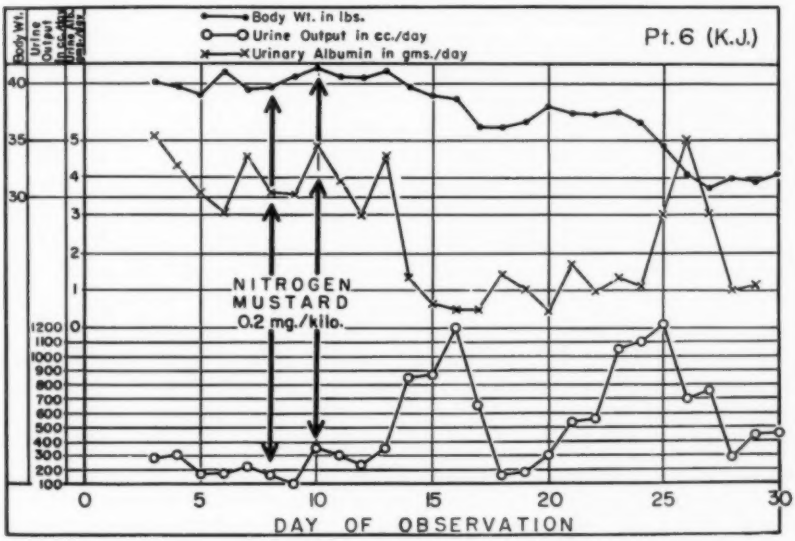


Fig. 4.—Diuretic response of Patient 6 (K. J.) to nitrogen mustard therapy.

individuals studied, including this patient, did there occur a significant elevation of total serum protein or of serum albumin concentration antecedent to the onset of diuresis or for that matter even during the early period following diuresis.

*Response of Other Laboratory Criteria to Nitrogen Mustard Therapy.*—Studies of certain electrolytes were made on the blood of most of these patients but not systematically enough to justify detailed reports at this time. In general, it was found in these cases, as previously reported by others,[15] that the sodium and carbon dioxide values are lower than normal and the potassium values approximate the normal value. However, in this series of patients the serum chloride values have ranged in general somewhat below normal. This is in contrast to the general trend of values reported by McQuarrie and Ziegler,[15] although in their series many of the serum chloride values were observed to be low. In the present series of patients calcium and phosphorus values were normal in those individuals in whom they were determined.

Nitrogen mustard therapy appears to have little effect on serum electrolyte concentrations in most cases despite the occurrence of diuresis. In Patient 1, as illustrated in Fig. 1, the serum electrolyte values returned to-

ward normal following nitrogen mustard therapy. However, in the other patients studied this effect was not observed.

Serum cholesterol values were not apparently influenced by the administration of nitrogen mustard regardless of whether or not diuresis occurred. All patients studied had abnormally high serum cholesterol levels before and after the administration of this drug.

In general, blood urea nitrogen levels, although not markedly elevated initially, were diminished during the period following nitrogen mustard therapy as compared to the pretherapy period. This is interpreted as probably reflecting improved renal function in conjuction with the diuretic response to the drug. This assumption is in conformity with evidence presented by other workers.[16, 17]

## DISCUSSION

Eloquent testimony to the relative ineffectiveness of the various proposed modes of therapy of the nephrotic syndrome is provided by the large variety of such therapeutic regimens that have been advanced. A principal inherent difficulty encountered in any attempt to evaluate the results of therapy of this syndrome is presented by the capriciousness of the malady. The unpredictability of the time or extent of spontaneous diuresis renders certain identification of induced diuresis a nearly impossible task. However, during recent years several new agents in therapy have been demonstrated to be capable of inducing diuresis. These include adrenocorticotropic hormone,[16, 18-21] measles,[22] sodium and potassium salts,[23] concentrated human serum albumin,[17] and nitrogen mustard.[8-10] All of these agents have been shown to initiate diuresis at a predictable time in a high enough percentage of patients virtually to eliminate from consideration the possibility of these diureses being spontaneous and occurring on the basis of chance alone. Nitrogen mustard therapy does not uniformly produce diuresis, and in those patients in whom diuresis does result the reaccumulation of edema quite frequently occurs. Yet, the results in the present series and in other reported experience[8-10] with this approach to therapy of the nephrotic syndrome have been relatively gratifying.

While inviting enticing speculation, the rationale for nitrogen mustard therapy of the nephrotic syndrome originally advanced by Chasis, Goldring, and Baldwin[8] is not established. Although there does exist a considerable body of highly suggestive evidence that, as first suggested by Schick in 1907,[24] antigen-antibody mechanisms may be etiological[1-7, 25-30] in glomerulonephritis and lipoid nephrosis, there exists no conclusive proof of this. Likewise the mechanism of the influence of nitrogen mustard on hypersensitivity reactions is incompletely understood, although recent investigations have helped considerably toward clarifying this relationship. Localization of antigens in tissues has been demonstrated to occur.[2, 5, 31-33] Hawn and Janeway[34] demonstrated that injection into rabbits of bovine serum albumin and of bovine serum globulin produced different pathological and immunological responses and postulated on the basis of their data that the differences resulted from selective localization of the antigens at different tissue sites because of their differences in chemical

composition, that after tissue fixation antibody is brought to such sites by lymphocytes and monocytes or is elaborated by fixed cells at these local sites, and that the resultant interaction between antibody and antigen at these sites of antigen fixation results in local tissue changes of inflammation and repair. This hypothesis is based in part on the evidence summarized by Longcope[35] that antigen-antibody reactions must take place within cells or upon cell surfaces in order to produce symptoms.

The lesions observed in the animals of Hawn and Janeway[34] were similar to those described in patients dying with serum sickness,[36] which was originally postulated by von Pirquet and Schick[37] to be based upon an antigen-antibody reaction. This hypothesis has since been substantiated.[38] It has recently been demonstrated that nitrogen mustard administration will inhibit antibody production and will inhibit the development of hypersensitivity reactions.[11, 12]

Becker[39] has been able to inhibit the Shwartzman phenomenon, likewise, by the use of nitrogen mustard. This phenomenon described by Shwartzman[40, 41] is presumed to be closely related to the basic mechanism underlying the production of a variety of clinical syndromes in which vascular lesions are a prominent feature.[42] Schlang[43] has confirmed the inhibitory effect of nitrogen mustard on the Shwartzman reaction and presented evidence interpreted as indicating that this inhibition results from a systemic rather than local effect. This suggestion is of interest in view of the demonstrated ability of ACTH[42] and of cortisone[44] to inhibit the occurrence of this phenomenon. In this light it is interesting to recall the similar effects mentioned above of nitrogen mustard, of ACTH, and of measles on patients with the nephrotic syndrome. More recent and detailed studies by Stetson and Good[45] have again confirmed the inhibition of the Shwartzman phenomenon by nitrogen mustard. They present impressive evidence that local accumulation of polymorphonuclear leukocytes plays a primary role in the development of the lesions characteristic of this phenomenon and that inhibition of the phenomenon by nitrogen mustard is related to and dependent upon the leukopenia resulting from administration of this drug and the related failure of accumulation of polymorphonuclear leukocytes at the site of "preparation" (or initial injection).

From the above discussion it may be concluded that if the mechanisms involved in the pathogenesis of the nephrotic syndrome be related to antigen-antibody reactions or to the Shwartzman phenomenon, experimental evidence suggests that nitrogen mustard should be of value in therapy. Even if the mechanisms involved be not related to either of these phenomena, clinical evidence indicates that nitrogen mustard is at least of moderate value in therapy. It appears that this type of therapy will induce diuresis in a high percentage of patients treated (69 per cent in the present series). Although the production of diuresis in many instances is important to the patient and to his parents, it may not indicate any significant alteration of the basic disease process. Observations reported here do not conclusively substantiate the occurrence of any such fundamental physiological alterations.

SUMMARY

1. Nine patients suffering with the nephrotic syndrome were administered thirteen courses of nitrogen mustard therapy. In nine instances diuresis occurred.

2. The chemical changes which occurred in response to this therapy are presented and discussed.

3. Rationale for this approach to therapy of the nephrotic syndrome is presented and discussed.

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# THE NEPHROTIC SYNDROME IN CHILDREN

## II. Observations Concerning Certain Acute Phase Reactants

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IN ADDITION to the classical features observed in patients with the nephrotic syndrome (albuminuria, hypoproteinemia, anasarca, ascites, and hyperlipidemia) certain other chemical and physiological abnormalities recently have been found to occur consistently in such patients. These include increased concentration of the serum nonspecific hyaluronidase inhibitor,[1] increased rate of incorporation of $S^{35}$-labeled methionine into the serum proteins,[2] and decreased antistreptolysin-O titer in the serum with increased titer in the urine.[3] The serum mucoproteins have been observed to be present in increased concentration early in the course of the disease and late in the convalescent period but usually in decreased concentration during the active phase of the disease.[1]

Serum complement is decreased during the active course of the disease but returns to normal following diuresis.[4, 5] The occurrence of diuresis has been demonstrated to be without effect on the serum nonspecific hyaluronidase inhibitor concentration.[1]

Preliminary evidence has recently been presented that the serum nonglucosamine polysaccharide[6] and the serum hexosamine[7] levels are elevated in patients with lipoid nephrosis as well as in patients with acute glomerulonephritis. The present report is concerned with the results of a study of the serum nonglucosamine polysaccharides, hexosamines, and mucoproteins in patients with the nephrotic syndrome and with the effects of nitrogen mustard therapy of this syndrome on these acute phase reactants.

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This investigation was supported in part by a research grant from the National Institutes of Health, Public Health Service, Bethesda, Md.

### MATERIALS AND METHODS

The patients included in this study are nine children, ranging in age from 18 months to 9 years, with lipoid nephrosis, so designated on the basis of their clinical manifestations of anasarca, ascites, albuminuria, hypoproteinemia and hyperlipidemia without hypertension or hematuria, two children, 5 and 12 years of age, with the nephrotic syndrome secondary to a preceding typical glomerulonephritis, and one child 14 months of age with the nephrotic syndrome apparently occurring as a manifestation of Tridione toxicity. These children were observed in the pediatric departments of the Universities of Utah and Texas during the past several months. Nine of them have received at least one course of nitrogen mustard therapy and four have received two courses of such therapy. The clinical responses of patients 1 to 9 have been reported;[8] the numbers assigned to them in the present report correspond to those assigned to them in the previous report.

Nitrogen mustard ($HN_2$) was administered as previously described,[8] a single course of therapy consisting

of the administration of a dose of 0.2 mg. per kilogram of body weight on each of two successive days. Serum nonglucosamine polysaccharides were determined by the method of Shetlar, Foster, and Everett,[9] serum hexosamines by the method of Shetlar, Foster, Kelly, and Everett,[10] and serum mucoproteins as in studies previously reported.[1, 11]

TABLE I. ACUTE PHASE REACTANTS IN PATIENTS WITH THE NEPHROTIC SYNDROME

| PATIENT | DIAGNOSIS | AGE | SEX | ESR* | MPT† (MG. %) | NGP† (MG. %) | HA† (MG. %) |
|---|---|---|---|---|---|---|---|
| 1 | Lipoid nephrosis | 2 yr. | F | 41 | 0.7 | 102 | 89 |
| 2 | Nephrotic phase glomerulonephritis | 5 yr. | F | 48 | 1.0 | 168 | 97 |
| 3 | Lipoid nephrosis | 9 yr. | M | 35 | 3.1 | 134 | 101 |
| 4 | Lipoid nephrosis | 3 yr. | M | 44 | 2.7 | 169 | 108 |
| 5 | Lipoid nephrosis | 3 yr. | M | 52 | 2.9 | 111 | 111 |
| 6 | Lipoid nephrosis | 4 yr. | M | 44 | 1.2 | 189 | 81 |
| 7 | Nephrotic phase glomerulonephritis | 12 yr. | F | 59 | 2.5 | 148 | 57 |
| 8 | Lipoid nephrosis | 18 mo. | M | 43 | 1.8 | 155 | 93 |
| 9 | Nephrosis ± Tridione | 14 mo. | M | 42 | 1.3 | 97 | 110 |
| 10 | Lipoid nephrosis | 6 yr. | F | 40 | 2.2 | 102 | 84 |
| 11 | Lipoid nephrosis | 8 yr. | M | 43 | 1.0 | 154 | 89 |
| 12 | Lipoid nephrosis | 3 yr. | M | 65 | 3.6 | 158 | 98 |
| | | | | Mean = | 2.0 | 140.6 | 93.2 |
| | | | | S.E.M. = | ±0.29 | ±8.85 | ±4.35 |

*Wintrobe method.

†*Normal values:*

| | | Mean ± S.E.M. |
|---|---|---|
| MPT = Mucoproteins[11] | | 2.49 ± 0.06 |
| NGP = Non-glucosamine polysaccharides[9] | | 114 ± 3.2 |
| HA = Hexosamines[7] | | 54 ± 1.8 |

## OBSERVATIONS

Table I shows the serum levels of nonglucosamine polysaccharides, hexosamines, and mucoproteins, and the erythrocyte sedimentation rates observed during the active phase of the nephrotic syndrome in the twelve children included in this study. From these data it may be seen that the erythrocyte sedimentation rates and the serum hexosamine levels are characteristically elevated and the serum mucoprotein levels decreased in this group of patients. The erythrocyte sedimentation rate is abnormally high in each of these patients while the serum hexosamine level is above normal in all but one, that one being

TABLE II. EFFECT OF NITROGEN MUSTARD INDUCED DIURESIS ON ERYTHROCYTE SEDIMENTATION RATE, NONGLUCOSAMINE POLYSACCHARIDES, AND MUCOPROTEINS

| PATIENT | DATE | WT. | ESR | NGP* | HA† | MPT‡ |
|---|---|---|---|---|---|---|
| 1 | 9/27/51 | 35½ | 41 | 101 | 89 | 0.84 |
| | 9/28/51 | 35½ | | 98 | 87 | 0.67 |
| | Nitrogen mustard given (0.2 mg./K) on 10/ 2/51 and 10/ 3/51 | | | | | |
| | 10/ 8/51 | 36¾ | 24 | 108 | 104 | 1.2 |
| | 10/13/51 | 36½ | 67 | 91 | 83 | 0.67 |
| | 10/17/51 | 37¼ | | 100 | 109 | 1.0 |
| | 10/23/51 | 38½ | | 131 | 101 | 0.84 |
| 2 | 10/27/51 | 40¾ | 48 | 130 | 96 | 1.0 |
| | 10/30/51 | 41 | 36 | 168 | 92 | 0.67 |
| | Nitrogen mustard given (0.2mg./K) on 11/ 2/51 and 11/ 7/51 | | | | | |
| | 11/12/51 | 40½ | 40 | 174 | 103 | 1.8 |
| | 11/16/51 | 40½ | | 173 | 109 | 0.34 |
| | 11/21/51 | 36¾ | | 165 | 95 | 1.7 |
| | 11/24/51 | 36½ | | 167 | 98 | 1.8 |
| | 12/ 8/51 | 34¾ | 36 | | | |
| 3 | 6/ 1/50 | 79 | 35 | 134 | | 3.1 |
| | 6/ 5/50 | 76 | 35 | | 101 | 3.1 |
| | Nitrogen mustard given (0.2 mg./K) on 6/ 5/50 and 6/ 6/50 | | | | | |
| | 6/ 8/50 | 75¾ | 50 | | | |
| | 6/16/50 | 69¾ | 52 | 135 | 99 | 2.5 |
| | 6/23/50 | 79½ | 52 | 104 | 93 | 2.2 |
| | 6/26/50 | 72½ | | 106 | 96 | 3.2 |
| | 6/30/50 | 68½ | 50 | 127 | | |
| | 7/ 3/50 | 64½ | | 108 | 112 | 2.9 |
| | 7/20/50 | 59 | | 113 | 106.5 | 4.6 |
| | 8/30/50 | 63 | | 146 | 98 | 5.1 |
| | 8/24/50 | 61 | | 106 | 73 | 4.8 |
| | 11/16/50 | | 14 | 80 | 57 | 5.3 |
| 4 | 10/27/51 | 33 | | 166 | 105 | 3.2 |
| | 10/30/51 | 34 | 45 | 169 | 108 | 2.7 |
| | Nitrogen mustard given (0.2 mg./K) on 11/ 6/51 and 11/ 7/51 | | | | | |
| | 11/ 8/51 | 30¾ | 44 | | | |
| | 11/12/51 | 29 | 45 | 178 | 105 | 2.0 |
| | 11/16/51 | 27½ | | 176 | 110 | 2.8 |
| | 11/21/51 | 29½ | | 171 | 108 | 1.5 |
| | 11/24/51 | 30 | | 164 | 103 | 1.3 |
| 5 | 10/20/50 | 45 | 52 | 111 | 111 | 2.9 |
| | Nitrogen mustard given (0.2mg./K) on 10/27/50 and 10/28/50 | | | | | |
| | 10/30/50 | 47¼ | | 92 | 85 | 2.8 |
| | 11/ 3/50 | 42¾ | 57 | 113 | 96 | 3.5 |
| | 11/ 6/50 | 41¼ | 58 | 121 | 80 | 4.0 |
| | 11/10/50 | 36 | 60 | 97 | 98.8 | 4.9 |
| 6 | 4/11/51 | 40¼ | 22 | 178 | 81 | 1.2 |
| | 4/16/51 | 39½ | 44 | 189 | 98.8 | 0.8 |
| | 4/18/51 | 40½ | 50 | 110 | 87 | 0.8 |
| | 4/20/51 | 40½ | 44 | | | 1.0 |
| | Nitrogen mustard given (0.2 mg./K) on 4/20/51 and 4/21/51 | | | | | |
| | 4/25/51 | 38¾ | 53 | 105 | 59 | 1.2 |
| | 4/27/51 | 36¼ | 52 | 106 | 98.8 | 1.2 |
| | 4/30/51 | 37½ | 52 | 113 | 108.8 | 1.4 |
| | 5/ 2/51 | 37½ | 52 | 128 | 58 | |
| | 5/ 9/51 | 32 | 52 | 109 | 110.5 | |
| | 5/11/51 | 33 | 53 | 99 | 97.5 | 1.8 |

*NGP = Nonglucosamine polysacchardies.
†HA = Hexosamines.
‡MPT = Mucoproteins.

a child with a history of chronic glomerulonephritis with recent development of manifestations of the nephrotic syndrome. The mean serum hexosamine level is 93.2 mg. per cent, a value which is considerably higher than that of 78 mg. per cent taken as the upper limit of normal.[7] The serum nonglucosamine polysaccharide levels, however, are observed to be within normal limits in five of the twelve patients studied. On the other hand, in the other seven patients these values are markedly elevated. The mean value of 140.6 mg. per cent is at the upper limit of the normal range.[6] The mean serum mucoprotein value of 2.0 mg. per cent is distinctly less than the normal value.[11]

It was previously observed that, in general, children suffering with lipoid nephrosis have decreased serum concentrations of mucoproteins but that very early in the course of the disease and also late in its course this concentration may be higher than normal. The data obtained in the present study are in conformity with this. Patients 3, 4, 5, and 12, whose serum mucoprotein levels are observed to be somewhat higher than the mean normal value of 2.5 mg. per cent, are individuals observed early during their first episode of lipoid nephrosis. Patient 3, as shown in Table II, exhibited a depression of his serum mucoprotein level later in the course of his disease. Still later after the onset of his illness, when he had been edema-free for several months, when his nonglucosamine polysaccharide level had decreased, and when his erythrocyte sedimentation rate and hexosamine level had become normal, his mucoprotein level was observed to have increased to a maximum value of 5.3 mg. per cent.

Patient 5, who also had a rather high initial level of serum mucoprotein, likewise exhibited an elevation of this value to even higher levels following the occurrence of diuresis. Patient 4, on the other hand, who had a high initial serum level of mucoprotein showed a progressive decrease in this level despite the administration of nitrogen mustard and the occurrence of a moderate diuresis. It is interesting that in each of these cases mentioned if the serum nonglucosamine polysaccharides and hexosamine levels have decreased following the administration of nitrogen mustard, the serum mucoprotein level has increased, and if the former have failed to decrease, the serum mucoprotein level has remained low or become progressively lower.

The erythrocyte sedimentation rate has been virtually unaffected by nitrogen mustard therapy in all cases. In patient 3 it remained unchanged for a considerable period of time after nitrogen mustard had been administered. However, several months after the administration of nitrogen mustard when the child had been virtually free of edema and of other manifestations of the nephrotic syndrome for four months, the erythrocyte sedimentation rate was observed to be normal.

No consistent pattern of response of serum nonglucosamine polysaccharide or hexosamine levels to nitrogen mustard therapy is observed in this series of patients. Patient 6, who had elevated nonglucosamine polysaccharide levels initially, exhibited a rapid decrease in these values to within normal limits. This decrease, however,

occurred before the administration of nitrogen mustard so cannot be attributed to that therapy. Patient 3 exhibited decreases to normal of both nonglucosamine polysaccharide and hexosamine values during his post-therapy period of observation. However, in this case the response of these serum levels was not immediate but occurred several months after the diuretic response.

## DISCUSSION

Observations of decreased serum levels of mucoprotein during the active phase of the nephrotic syndrome and of increased levels early and very late in the course of the disease are in agreement with observations previously reported concerning a different series of patients.[1] The explanation of these findings advanced at the time of this previous report, namely, that mucoproteins are produced at a greater than normal rate and would be present in the serum in greater than normal concentration were it not for leakage of these substances into the urine through damaged glomeruli, appears plausible. In patients with the nephrotic syndrome the serum protein levels are decreased despite an apparently more rapid rate of protein formation than in the normal individual.[2] The serum levels of albumin and gamma globulin are selectively decreased more than those of alpha and beta globulins since the former two have smaller molecular dimensions.[12]

The serum concentrations of mucoproteins, molecules of relatively small size,[13, 14] would probably therefore be expected to be reduced even more drastically than those of other serum proteins. That the mucoproteins might be produced at a greater than normal rate and yet be present in the serum in lower than normal concentrations is a suggestion not without precedent; this same situation has been demonstrated to exist with respect to the concentration of antistreptolysin-O.[3] The elevations of the serum nonspecific hyaluronidase inhibitor,[1] nonglucosamine polysaccharides, and hexosamines in patients with the nephrotic syndrome would likewise suggest that were it not for increased urinary losses mucoproteins would be present in the serum of these patients in increased concentration since the situations in which all of these acute phase reactants are found to be elevated[6, 7, 11, 15] are otherwise quite similar.

Elevation of acute phase reactants in patients with the nephrotic syndrome constitutes suggestive evidence of disturbed adrenal cortical function in such patients. It has been demonstrated[16] that the hyaluronidase inhibitor level in the serum is under the control of an adrenal mechanism. Results of similar studies, now in progress, indicate that the mucoprotein, nonglucosamine polysaccharide, and hexosamine levels are controlled by similar mechanisms.[17] The persistence of elevations of the serum levels of these acute phase reactants as well as of the erythrocyte sedimentation rate after the occurrence of diuresis probably indicates, as has been borne out by repeated clinical observations, that the presence or absence of edema in these patients is of little significance with regard to evaluation of the status of the basic, underlying metabolic disturbance. It might also be deduced, as a corollary of the above statement, that since nitrogen

mustard therapy of the nephrotic syndrome does not provoke consistent changes in the patterns of the erythrocyte sedimentation rate and acute phase reactants it probably does little to alter the fundamental disturbances of the patient's physiology which manifest themselves as symptoms and signs of the nephrotic syndrome.

## SUMMARY

1. The serum levels of nonglucosamine ploysaccharides, hexosamines, and mucoproteins have been studied in twelve children with the nephrotic syndrome.

2. Serum hexosamine levels are found to be elevated consistently in patients with this syndrome while serum nonglucosamine polysaccharide levels are elevated in only some of the patients.

3. Serum mucoproteins are elevated early and late in the course of illness of these patients but are decreased below normal in patients who have a well-established active phase of the disease.

4. Nitrogen mustard therapy has little effect on these chemical evidences of disturbed metabolism in patients with the nephrotic syndrome.

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# THE EFFECTS OF MAGNESIUM SULFATE ON RENAL FUNCTION IN CHILDREN WITH ACUTE GLOMERULONEPHRITIS

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IN A previous publication concerning the influence of magnesium sulfate on renal hemodynamics in normal children, we have mentioned the direct or indirect association of generalized arteriolar spasm with the complications of acute hemorrhagic nephritis.[1] An historical summary of the important contributions concerning the antispasmodic effect of magnesium sulfate was included. In these normal children we demonstrated that parenteral administration of magnesium sulfate caused a significant alteration in the tubular excretory capacity for para-aminohippurate (PAH) and exerted no significant influence on other measured functions. The following report includes the results of quantitative measurements of renal function in children with acute nephritis and hypertension before and during magnesium sulfate therapy. This problem was undertaken in order to supply additional information concerning the action and usefulness of this compound.

## METHODS AND MATERIALS

Six children between the ages of 5 and 9 years with a diagnosis of acute hemorrhagic glomerulonephritis were used in this study. Findings of the disease such as gross and microscopic hematuria, albuminuria, oliguria, varying degrees of edema, and an elevation of blood presure ranging from 125 to 169 mm. Hg systolic and 92 to 110 mm. Hg diastolic were present in all cases. According to the history, the duration of illness ranged from two to six days before hospitalization.

Control clearances (mannitol and para-aminohippurate) were done soon after admission to the hospital and before administration of magnesium sulfate. Clearances were again performed after the intramuscular administration of magnesium sulfate in doses of 100 mg. per kilogram of body weight every four hours for periods of eighteen to twenty-four hours. Blood pressure was determined at frequent intervals during the interim between clearances and at more frequent intervals during the clearances. The technical procedure followed in performing the clearances has been described in a previous publication.[2] The analytical methods of Corcoran and Page[3] were used for determining mannitol, and para-aminohippurate was determined by the method of Smith and associates.[4] Serum magnesium levels were determined by a modification of the method of Denis.[5]

## RESULTS AND DISCUSSION

Individual and summarizing data obtained during this study as well as average values previously reported for normal children[1] are recorded in Table I. All clearance values have been cor-

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This study was supported by a research grant-in-aid from the National Heart Institute of the National Institutes of Health, Public Health Service.

rected for 1.73 square meters of body surface area utilizing the formula of DuBois and DuBois.[6]

Serum magnesium levels before therapy ranged from 1.1 to 2.2 meq. per liter and from 2.9 to 4.4 meq. per liter at the time of the second clearance. A comparison of the blood pressures at the time of the control clearances with those at the time of the second clearances reveals a reduction in systolic pressure ranging from 10 to 30 mm. Hg and a reduction in diastolic pressure from 2 to 36 mm. Hg. We observed no definite quantitative correlation between serum magnesium level and the reduction in blood pressure, an observation which has also been made on a number of other patients not included in this paper. This factor along with the unpredictable duration of action as well as the apprehension associated with the pain during and following the intramuscular injection of magnesium sulfate leaves much to be desired from the standpoint of its being an ideal therapeutic agent.

Reference to Table I clearly demonstrates that the glomerular filtration rate (GFR), effective renal plasma flow (ERPF), and tubular excretory capacity for para-aminohippurate (Tm [PAH]) were reduced in these patients with nephritis.

The GFR before magnesium sulfate therapy ranged from 58 to 113 c.c. per minute with a mean of 88.8 c.c. per minute, and represents a definite reduction when compared to the mean value of 131 c.c. per minute for normal children. The GFR was usually not influenced by magnesium sulfate. In one case (J. L. C.) there was an increase, and in another (J. C.), a substantial decrease. The mean value during magnesium sulfate therapy is similar to that of the control periods. There was no marked change in the GFR/Tm (PAH) ratio although in general there was a tendency for this fraction to increase.

The ERPF before magnesium therapy ranged from 390 to 747 c.c. per minute with a mean of 527 c.c. per minute. This represents an appreciable decrease in ERPF when compared to the mean value for normal children. Unlike results obtained in normal children, the ERPF in these patients was definitely increased during administration of magnesium sulfate. ERPF during therapy ranged from 462 to 891 c.c. per minute, with an average of 635 c.c., which incidentally approaches very closely the value for the normal children. When analyzed statistically this was found to be significant (critical ratio 3.21*) and is the only measured variable found to be significantly altered in this series. The effect of magnesium on the tone of the renal arterioles is apparently more pronounced when vascular spasm exists. This increased ERPF during magnesium therapy with no appreciable change in GFR results in a substantial decrease in the filtration fraction (Table I). Although no increase in GFR was associated with the relief of renal vascular spasm, the increase in plasma flow and the corresponding increase in blood flow would appear to be beneficial by promoting healing and improving nutrition in the diseased

*Critical ratio = mean difference ÷ standard error of the difference. Standard error of the difference $\frac{\sqrt{\frac{\Sigma d^2}{N}}}{\sqrt{N}}$ in which N = the number of patients and $\Sigma d^2$ the sum of the squared deviations of the difference between the values obtained during the control and subsequent clearance in each patient from the mean difference.

TABLE I. RENAL CLEARANCES IN CHILDREN WITH ACUTE GLOMERULONEPHRITIS

| NAME | AGE | BODY SURFACE AREA (SQ.M.) | NPN (MG. %) | CORRECTED TO 1.73 SQ.M. SURFACE AREA | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | GFR (C.C./MIN.) | | ERPF (C.C./MIN.) | | Tm (PAH) (MG./MIN.) | |
| | | | | CONTROL | AFTER $MgSO_4$ | CONTROL | AFTER $MgSO_4$ | CONTROL | AFTER $MgSO_4$ |
| C. Ch. | 6 | 0.86 | 32 | 70 | 78 | 536 | 608 | 97 | 78 |
| C. Cu. | 5 | 0.81 | 24 | 111 | 100 | 452 | 553 | 102 | 100 |
| R. L. Wa. | 5 | 0.79 | 24 | 91 | 98 | 390 | 462 | 76 | 85 |
| M. We. | 7 | 0.97 | 36 | 90 | 99 | 747 | 891 | 79 | 82 |
| J. C. | 7 | 0.77 | 25 | 113 | 84 | 557 | 555 | 72 | 68 |
| J. L. C. | 9 | 1.25 | 38 | 58 | 98 | 478 | 743 | 65 | 75 |
| Average | | | | 88.8 | 92.8 | 527 | 635 | 81.8 | 83 |
| Normal average | | | | 131 | 122 | 627 | 629 | 94 | 108 |

kidney. This is the only beneficial effect we can attribute to magnesium insofar as renal hemodynamics are concerned. However, the relief of generalized arteriolar spasm is responsible for the reduction of blood pressure and aids in the prevention of cardiac failure, encephalopathy, and other undesirable sequelae of hypertension.

The Tm (PAH) in these nephritic patients before treatment was reduced, ranging from 65 to 102 mg. per minute, with an average of 81.8 mg. per minute, compared to an average of 94 mg. per minute in normal children. An increase in the serum magnesium resulted in no consistent alteration in this function and the range and average values for Tm (PAH) were similar in all cases during the two clearance periods. It is interesting to note that the Tm (PAH) in normal children was significantly increased by magnesium sulfate. The ERPF/Tm (PAH) in the nephritic patients was increased during magnesium sulfate administration whereas there was a slight reduction in this ratio in normal children. This is explained on the basis of relief of renal arteriolar spasm by magnesium in the patients with nephritis without alteration in the Tm (PAH). It is logical to suspect that edema, etc., of the tubules is in a measure responsible for the lack of influence of magnesium on Tm (PAH) in patients with nephritis.

## SUMMARY AND CONCLUSIONS

1. Renal hemodynamics (mannitol and PAH clearances) have been performed on six patients with acute hemorrhagic nephritis with hypertension before and during therapy with magnesium sulfate.

2. Serum magnesium levels of 2.9 to 4.4 meq. per liter were attained with a reduction in systolic blood pressure of 10 to 30 mm. Hg and in diastolic pressure of from 2 to 36 mm. Hg.

3. All measured renal functions were reduced by the nephritic process.

4. The only significant alteration in renal hemodynamics during magnesium therapy was an increase in ERPF from an average value of 527 c.c. per minute to an average of 635 c.c. per minute.

5. It is believed that the increase in ERPF as well as the reduction in systemic blood pressure is attributable to generalized arteriolar relaxation.

We wish to acknowledge with gratitude the technical assistance of Lois Jones, B.S.

BEFORE AND DURING ADMINISTRATION OF MAGNESIUM SULFATE

| FILTRATION FRACTION (GFR × 100/ERPF) | | GFR/Tm (PAH) | | ERPF/Tm (PAH) | | SERUM MAGNESIUM (MEQ./L.) | | MEAN BLOOD PRESSURE DURING CLEARANCE (MM. HG) | |
|---|---|---|---|---|---|---|---|---|---|
| CONTROL | AFTER $MgSO_4$ | CONTROL | AFTER $MgSO_4$ | CONTROL | AFTER $MgSO_4$ | CONTROL | AFTER $MgSO_4$ | CONTROL | AFTER $MgSO_4$ |
| 13.00 | 12.85 | 0.72 | 1.00 | 5.55 | 7.80 | 1.9 | 4.4 | 125/97 | 112/90 |
| 24.60 | 18.10 | 1.09 | 1.00 | 4.43 | 5.53 | 2.2 | 3.6 | 140/100 | 122/90 |
| 23.31 | 21.20 | 1.20 | 1.15 | 5.15 | 5.45 | 1.3 | 2.9 | 140/110 | 110/80 |
| 12.05 | 11.10 | 1.14 | 1.21 | 9.45 | 10.88 | 1.6 | 3.2 | 142/90 | 132/88 |
| 20.30 | 15.15 | 1.43 | 1.23 | 7.75 | 8.16 | 1.1 | 2.9 | 153/92 | 128/56 |
| 12.15 | 13.20 | 0.89 | 1.31 | 7.35 | 9.90 | 1.8 | 3.9 | 169/100 | 148/91 |
| 17.57 | 15.28 | 1.08 | 1.15 | 6.61 | 7.96 | 1.65 | 3.48 | 145/98 | 125/83 |
| 21.5 | 18.8 | 1.41 | 1.14 | 6.7 | 6.3 | 1.15 | 3.2 | ---- | ---- |

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# ADRENOCORTICOTROPIC HORMONE IN THE CONTROL OF ACUTE INFANTILE BRONCHIOLITIS

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THE treatment of acute infantile bronchiolitis is essentially supportive rather than curative, intended to control anoxia during the course of bronchiolar obstruction. Although it seems probable that most instances of this syndrome, particularly in epidemic form, are related to primary atypical pneumonia, no specific etiology has been discovered, nor have antibiotic agents intended to attack its possibly viral origin proved to be of distinct value. Agents capable of liquefying bronchiolar exudate, antispasmodics, and vasoconstrictors have been relied upon to reduce bronchiolar obstruction, and, particularly in the case of the first mentioned, have been successful in most instances. However, despite such supportive measures progressive bronchiolar obstruction occasionally results in irreversible anoxic injury to the central nervous system, dehydration and renal damage, respiratory alkalosis (or rarely acidosis),[1] cor pulmonale,[2] and death. Thus, there exists a distinct need for an agent which, superimposed upon presently available measures, is capable of reversing the severe obstructive disease which results in such complications. Adrenocorticotropic hormone has been clearly shown to inhibit exudative inflammatory reactions to a variety of agents and has been demonstrated to reduce bronchiolar obstruction in allergic asthma as well as in chronic emphysematous states.[3] The present controlled study of the effect of adrenocorticotropic hormone in alternate cases of an epidemic of bronchiolitis of infancy was undertaken to determine the response of the severe bronchiolar obstruction of this disease to the administration of this anti-inflammatory agent.

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## MATERIAL AND METHODS

The material for this study consisted of nineteen consecutive patients with acute infantile bronchiolitis admitted to the pediatric section, William Beaumont Army Hospital, during a small epidemic of this disease occurring between January and April, 1952. All cases occurred in previously well, white infants from the same good socioeconomic status. There was at least chronological correlation with a troop epidemic of primary atypical pneumonia, but direct contact between cases of each syndrome could not be established.

A large number of infants with mild to moderate acute bronchiolitis were seen as outpatients and many others were hospitalized with primary atypical pneumonia and related syndromes, but only those patients in whom acute febrile bronchiolar obstruction with dyspnea and emphysema required admission and oxygen-humidity therapy were selected for study. No specific etiological diagnosis could be estab-

lished in these patients; cold hemagglutinins were absent in all cases, throat cultures revealed normal flora or occasionally a small percentage of beta hemolytic streptococci, and tuberculin and coccidioidin skin tests were negative. These findings, the presence of moderate neutrophilic leukocytosis, the presence of stool trypsin, and the absence of recurrent attacks eliminated the *Hemophilus influenzae* or pertussis and systemic mucoviscidosis as causes of the bronchiolar inflammation.

Alternate admissions demonstrating the above pattern were treated with ACTH, 20 mg. every eight hours, intramuscularly, subsequent to a twelve- to eighteen-hour period of hospital stabilization (nine patients), or were retained as controls (ten patients). All patients received increased humidity, oxygen (except two—one in each group), intramuscular penicillin and streptomycin (as prophylaxis against secondary infection), and supportive parenteral fluid and electrolyte therapy (as indicated). No other drugs, antibiotics, antispasmodics, or expectorants were utilized. The use of a stabilization period essentially eliminated the significant effects of usual therapy and permitted an evaluation of the effect of ACTH alone upon the production of remissions in the second hospital day. ACTH was initiated in this manner and was continued in the same dosage for seventy-two hours in all cases with but two exceptions: in one case cortisone, 300 mg. daily for three days, intramuscularly, was substituted for ACTH, and in one case ACTH was commenced after a six-hour stabilization period because of the child's desperate condition.

Evaluation of the total course of the disease state and of the production of remissions during the second hospital day was accomplished by the daily (on the second hospital day, thrice daily) record by the same observer of the character and degree of dyspnea, suprasternal and costal retractions, cyanosis, cough, tachypnea, râles, expiratory prolongation, diminution of breath sounds, and fever, as well as the duration of oxygen-humidity administration. Daily fasting total eosinophil counts were obtained prior to and during ACTH therapy which demonstrated a greater than 50 per cent fall in circulating eosinophils subsequent to ACTH in all instances. No significant side reactions attributable to ACTH were detected; daily record of body weight showed no consistent alterations. All patients recovered completely in an average of five days after admission.

TABLE I. COMPARABILITY OF THE TREATED AND UNTREATED GROUPS

| | ACTH GROUP | CONTROL GROUP |
|---|---|---|
| Age—average, in months | 8.2 | 7.1 |
| Sex—percentage of males | 55.5% | 60% |
| Duration of disease—prior to admission, in days average | 3.2 | 3.0 |
| Cyanosis—percentage demonstrating | 66.6% | 60% |
| Fever—greater than 101° F., percentage demonstrating | 88.8% | 60% |
| Radiological evidence of pneumonitis—percentage demonstrating | 33.3% | 40% |

Table I shows the excellent comparability of the treated and untreated groups. Although two patients in each group were over one year of age, the majority were less than 6 months, and the average of each group approximated 7 to 8 months. The average duration of the disease prior to admis-

sion was almost identical in the two groups, indicating the validity of determining the effect of therapy by analysis of the duration of the subsequent course. The severity of the bronchiolitis as evidenced by the frequency of cyanosis, fever greater than 101° F., and the presence of radiological evidence of pneumonitis is closely comparable in the two groups with a slightly greater degree of bronchiolar obstruction in the treated. This, of course, provides an enhanced opportunity for the demonstration of any ACTH effect.

### CASE REPORTS

The following cases are illustrative of the dramatic response of the dyspnea of acute bronchiolitis to adrenocorticotropic hormone which occurs under certain circumstances.

CASE 1.—D. S., a 3-month-old white male, was admitted to the pediatric section, William Beaumont Army Hospital, because of fever and respiratory difficulty with cough, tachypnea, suprasternal and costal retractions, and cyanosis of two days' duration. Physical examination revealed a tired, restless, moderately cyanotic infant with a temperature of 101.8° F., a respiratory rate of 70 per minute, numerous fine moist râles in all lung fields, generally diminished breath sounds with prolonged expiration, and hyperexpansion and hyperresonance of the thorax. The white blood count was 10,400 with 58 per cent neutrophils (8 per cent stabs), culture of the throat revealed 10 per cent beta hemolytic streptococci, no cold hemagglutinins were detected, and radiological examination of the chest revealed a small area of infiltration extending superiorly from the left hilum. Dyspnea and cyanosis became extreme as signs of bronchiolar obstruction, diminished breath sounds, prolonged expiration, and hyperresonance increased despite oxygen, humidity, and antibiotics. ACTH, 20 mg. every eight hours, intramuscularly, was commenced twenty-four hours after admission. Within four hours dyspnea, cyanosis, and retractions were markedly reduced, the respiratory rate had fallen from 90 to 70 per minute, breath sounds were readily audible, expiration but minimally prolonged, and hyperresonance was much decreased. Coarse rhonchi became apparent where none had existed, and with a respiratory rate of 40 per minute, the tight bronchiolar obstruction was scarcely apparent the following day. Uneventful disappearance of the residual cough, fever, tachypnea, and rhonchi followed over a seven-day period.

CASE 2.—F. H., 26-month-old white male, was admitted to the pediatric section, William Beaumont Army Hospital, because of fever and severe respiratory difficulty with cough, tachypnea, suprasternal and costal retractions, and cyanosis of thirty-six hours' duration. Physical examination revealed an exhausted, deeply cyanotic, infant with a temperature of 101.4° F., a respiratory rate of 100 per minute, almost completely absent breath sounds at both bases (markedly diminished elsewhere), and marked hyperexpansion and hyperresonance of the thorax. The white blood count was 9,300 with 66 per cent neutrophils (33 per cent stabs), a throat culture revealed normal flora, radiological examination of the chest revealed only emphysema, and no cold hemagglutinins were detected. Because of the desperate condition of the infant, ACTH, 20 mg. every eight hours, intramuscularly, was commenced six hours after admission when oxygen, humidity, and antibiotics had produced no improvement. Within four hours, cyanosis had disappeared, dyspnea was greatly decreased, the respiratory rate had fallen from 100 to 60 per minute, breath sounds were of normal intensity throughout, and resonance was only moderately increased. The chest suddenly seemed filled with coarse moist râles where none had been previously audible, and, by the following day, except for slight retrac-

tions of the costal margin and a respiratory rate of 50 per minute, all signs of bronchiolar obstruction had disappeared. The residual cough, fever, tachypnea, and rhonchi gradually disappeared during the following six days.

## RESULTS

Table II demonstrates the effect of adrenocorticotropic hormone combined with oxygen, humidity, prophylactic antibiotics, and parenteral fluids as compared with the effect of the latter measures alone upon the subsequent course of various qualitative manifestations of the total disease state. The average duration of these factors as given in the table is determined from the day of hospitalization rather than from the second day of hospitalization at which time adrenocorticotropic hormone was introduced and indicates the presence of the particular manifestation on a certain day without any indication of its severity beyond the lower limit indicated in the chart. The pathologically nonspecific factors, cough and fever, were certainly not benefited by therapy and their greater duration in the treated group again indicates the probably slightly greater severity of the disease in this group. The duration of symptoms, dyspnea, and signs of bronchiolar obstruction, retractions, cyanosis, tachypnea, râles, expiratory prolongation, and emphysema (in which is included the presence of diminished breath sounds, hyperexpansion, and hyperresonance of the thorax), was not significantly different in the two groups, which correlated analysis of the many facets of this state demonstrates. Measurement of the duration of necessary oxygen-humidity administration indicates the same lack of effect of adrenocorticotropic hormone on the total duration of bronchiolar obstruction.

TABLE II. EFFECT OF THERAPY: AVERAGE DURATION IN DAYS OF MANIFESTATIONS OF THE DISEASE STATE SUBSEQUENT TO HOSPITALIZATION

| | ACTH GROUP | CONTROL GROUP |
|---|---|---|
| Dyspnea | 3.5 | 3.6 |
| Retractions—suprasternal and costal | 1.9 | 3.0 |
| Cyanosis | 1.3 | 1.3 |
| Cough | 5.0 | 4.7 |
| Tachypnea—respiratory rate greater than 40 per minute | 5.2 | 4.7 |
| Râles | 3.5 | 3.2 |
| Expiratory prolongation | 1.8 | 3.2 |
| Emphysema | 3.4 | 3.0 |
| Fever—temperature greater than 99.6° F. | 3.6 | 2.9 |
| Oxygen and humidity administration | 5.4 | 4.8 |

TABLE III. EFFECT OF THERAPY: OCCURRENCE OF REMISSIONS OF DYSPNEA WITHIN TWENTY-FOUR HOURS OF THE INTRODUCTION OF THERAPY (THE SECOND HOSPITAL DAY)*

| | ACTH GROUP (%) | CONTROL GROUP (%) |
|---|---|---|
| Marked remission | 44.4† | 0 |
| Moderate remission | 55.5 | 50 |
| No remission | 0 | 50 |

*Subsequent to a twelve- to eighteen-hour period of stabilization with oxygen, humidity, and supportive care.

†Including one patient treated with cortisone.

However, as presented in Table III, a distinct effect of adrenocorticotropic hormone upon the degree of bronchiolar obstruction was apparent. In every instance, a remission in all of the signs and symptoms of bronchiolar obstruction as listed in Table II appeared within twenty-four hours of the introduction of adrenocorticotropic hormone. Although this also occurred at the same time (during the second hospital day) in 50 per cent of the control group, only in the treated

group did marked remissions occur and then in 44 per cent. A marked remission was considered to have occurred when an abrupt decrease in all signs of bronchiolar obstruction altered the course of disease from a state of marked anoxia to minimal dyspnea or from moderate anoxia to no dyspnea; a lesser but nevertheless distinct improvement in all signs of obstruction was considered to be a moderate remission. If any single manifestation of bronchiolar obstruction failed to improve, no remission was considered to have occurred. In but one instance did a slight relapse of the signs of obstruction appear subsequent to the three-day course of therapy although in every instance some evidence of disease persisted.

In each instance in which a marked remission was considered to have occurred with adrenocorticotropic hormone, severe respiratory difficulty with distinct anoxia was present and within four to eight hours had been reduced to minimal dyspnea. This response was produced in all severe cases that were treated (four). In the other treated patients moderate anoxia, indicated by dyspnea and frequently cyanosis, insufficient to be productive of dangerous complications, was followed, subsequent to therapy, by a moderate remission indistinguishable from the spontaneous remissions of the control group. In each of the severely anoxic infants, marked tachypnea, cyanosis, retractions, diminished to absent breath sounds, prolonged expiration, absence of râles, hyperexpansion and hyperresonance of the chest was followed, subsequent to therapy, by a dramatic decrease in tachypnea and retractions, disappearance of cyanosis, restoration of normal breath sounds, duration of expiration, expansion of the thorax, and the appearance of coarse moist râles where none had previously been detected. Presumably this signified the conversion of the tightly plugged, edematous, possibly spastically contracted, bronchiolar bed which permitted almost no air passage, except during inspiration, into a relaxed, open system filled with loose, but no longer obstructing, exudate. One instance of this reaction occurred subsequent to the administration of cortisone in place of adrenocorticotropic hormone. The presented case reports provide the clearest illustration of the character of this marked remission of severe bronchiolar obstruction.

## DISCUSSION

Although the clinical pattern of acute febrile expiratory obstruction with tachypnea, suprasternal and costal retractions, and emphysema has long been recognized as a distinct entity in infants, acute bronchiolitis, its correlation with or delineation from other acute respiratory infections has not been satisfactorily accomplished. This clinical syndrome has been described as "primary pneumonitis of infancy"[4] or as "primary atypical pneumonia of infancy,"[5] although in most instances only emphysema is apparent upon radiological examination. As in the cases presented herein, the presence or absence of radiological infiltrations seems immaterial to the pattern and course of the disease state. However, such infiltration and the epidemiological correlation with typical primary atypical pneumonia in older children and adults[6] indicate the possibility that acute bronchiolitis is the usual manifestation of primary atypical pneumonia in infants. Cold

hemagglutinins are rarely,[7] though occasionally,[8] detected in infants even when the clinical pattern and epidemiological correlation with primary atypical pneumonia seem close. Pathological study of primary atypical pneumonia in adults reveals that the disease is chiefly an exudative, necrosing bronchiolitis[9] and it is to be expected that in the minute bronchioles of infancy this will result in the clinical pattern of diffuse bronchiolar obstruction in contrast to the apparently localized pneumonitis of older patients.

The specific antiviral therapy of acute infantile bronchiolitis with aureomycin has been of questionable value.[8] Although early reports seemed to indicate that the broad spectrum antibiotics were effective in both infantile, childhood,[10] and adult[11] primary atypical pneumonia, recent good evidence[12] indicates that they are of no value. Thus, the probable correlation of acute bronchiolitis with primary atypical pneumonia, and the enhanced etiological delineation of the syndrome, is of no therapeutic value at present. The acute bronchiolar obstruction of the disease in infants remains unaffected by attempted antiviral therapy and requires control through alteration of the local inflammatory reaction.

Adrenocorticotropic hormone is known to inhibit the reactivity of tissue to a variety of injurious agents, chemical, bacterial, and antigenic.[3] In rheumatoid arthritis, biopsy subsequent to the administration of this drug, has shown a decrease in cellular exudate, vascularity, fibrin deposition, necrosis, and edema.[13] A marked decrease in the bronchiolar obstruction of allergic asthma, apparently due to the same reduction in tissue reactivity, rapidly follows adrenocorticotropic hormone therapy.[14] In chronic pulmonary fibrosis of varied etiology, this drug produces a rapid increase in oxygen diffusing capacity with decreased physiological venous admixture probably consequent to improved diffusion across the altered alveolar membrane and to improved ventilation of obstructed alveoli.[15] Kass, Ingbar, and Finland[16] have demonstrated a prompt remission in the clinical symptoms of two cases of adult virus pneumonia subsequent to adrenocorticotropic hormone administration. Thus, from both laboratory and clinical evidence, it would seem probable that this agent would reduce the inflammatory exudate, vascularity, necrosis, and edema of acute bronchiolitis, and, as in asthma and chronic pulmonary fibrosis, reduce ventilatory obstruction so that adequate oxygenation might be restored.

In the past this end has been accomplished chiefly through the use of agents which tend to liquefy the bronchiolar exudate thus preventing its inspissation and obstruction. The inhalation of water vapor, most effectively produced by a cold centrifugal humidifier, is highly effective and, in most instances, entirely sufficient for this purpose. The use of oxygen which has a marked drying and inspissating effect upon pulmonary secretions and which may obscure developing exhaustion must be closely observed and always covered by the simultaneous administration of water vapor. Carbon dioxide is also an excellent liquefying agent, but to avoid respiratory acidosis may only be used for short periods. It seems most effective when used to deliver antispasmodic, vasoconstrictive aerosols such as Neo-Synephrine which may themselves be of value in certain instances although it

is probably the carbon dioxide and water which exert the greater effect. Epinephrine and its derivatives, systemically administered, are of occasional value, indicating the probable presence of muscle spasm in some instances. Other liquefying agents such as potassium iodide and hydriodic acid are of value but are difficult to administer to infants. Most essential is the maintenance of adequate fluid and electrolyte balance not only for the control of respiratory alterations of pH and renal function, but to combat the great loss of water associated with hyperventilation and the consequent drying of the bronchiolar exudate. Postural drainage seems to be of little value and aspiration even through a tracheotomy (if some degree of high obstruction exists) is usually ineffective in benefiting the diffuse bronchiolar obstruction. In those cases which progress despite the above measures, anoxemia may be lessened by whole blood transfusion, but this may be hazardous in the probable presence of pulmonary interstitial emphysema with its consequent increased pulmonary vascular resistance and possible cor pulmonale.[2] Anoxic injury and edema of the central nervous system may be partially controlled by the use of anticonvulsants, and, occasionally, lumbar puncture to reduce intracranial pressure.

The occurrence of progressive bronchiolar obstruction, persistent anoxia, and possible cardiac failure unresponsive to any available therapy constitutes the residual danger of acute bronchiolitis which demands an additional and more potent protective agent. From the evidence presented herein it would appear that adrenocorticotropic hormone is such an agent, providing safety in the resolution of progressive bronchiolar obstruction when all other resources have failed. Indeed, it appears that it is precisely those instances of severe progressive bronchiolar obstruction, which unresponsive to all usual therapy seem certain to result in irreversible anoxia, that respond so distinctly to this agent. As demonstrated in this study adrenocorticotropic hormone has no effect upon the total duration of disease and its effect upon moderate bronchiolar obstruction is apparently no greater than that of the usual therapy. Thus, its routine use in acute infantile bronchiolitis is probably not indicated. However, in every instance, the hormone appears to reduce the exudate, edema, and vascularity of the bronchiolar wall, thereby restoring alveolar ventilation despite the persistence of the original exudate as loose debris rattling in the opened system. As a single administration seems to produce this full resolution of obstruction a shorter course of therapy or the administration of single doses as needed may provide entirely adequate control.

## SUMMARY

A controlled study of nineteen cases of acute infantile bronchiolitis is presented which indicates that adrenocorticotropic hormone is effective in the control of inflammatory bronchiolar obstruction.

This study was initiated consequent to the suggestions of Dr. Charles F. Rennick and Captain Albert G. Miller, M.C., United States Army. The enthusiastic cooperation of Captain Helmi Heikkila, A.N.C., United States Army, and the nursing personnel, Pediatric Section, William Beaumont Army Hospital, in the collection of data was invaluable. The assistance of First Lieutenant Marion L. Hanlon in the latter portion of the study is gratefully acknowledged.

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## Addendum

Since the preparation of this paper, the use of adrenocorticotropic hormone in the treatment of acute laryngotracheitis in preschool children has been reported (Turner, J. A., and Morgan, E. A.: Corticotropin [ACTH] in the Treatment of Acute Laryngotracheitis, Am. J. Dis. Child. 83: 440, 1952) In comparing the course of five treated and five untreated severely ill patients, these authors were unable to detect any effect of adrenocorticotropic hormone on the glottic and subglottic obstruction of this disease.

# FEBRILE CONVULSIONS

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IN 1949 I presented a report on the study of 128 children with a history of fever convulsions. This series represented 4 per cent of the 3,000 cases of childhood convulsions collected in twenty-five years of private and hospital practice, which were followed for from one to twenty-five years. It was, at that time, the largest series of "febrile convulsions" studied for the longest period of time with the aid of electroencephalography. An arbitrary definition was proposed, i.e., "A febrile convulsion is a major seizure with a loss of consciousness, precipitated by a non-specific fever of variable degree in a child with a potential convulsive disorder."[1]

Further study and observation of these cases and the addition of 174 more cases require a re-evaluation of the statistics and also of the conclusions.

Since my report Livingston has presented a series of 498 children with febrile convulsions.[2] These were all seen at the hospital at the time of the first convulsion. As in my series, Livingston did not include patients with evidence of infection of the central nervous system, such as meningitis, encephalitis, etc. His patients also had had no known previous convulsions. Livingston divided his cases into two groups:

*Group A.* Those patients who presented, at the time of their initial seizure, one or more of the following findings:

1. A prolonged convulsion (over one-half hour).
2. A focal convulsion.
3. Family history of epilepsy.
4. Specific electroencephalographic abnormalities.

*Group B.* Those patients who presented, at the time of their first seizure, only a short, generalized convulsion (one to five minutes).

Of the 297 patients in Group A, 276 (93 per cent) have developed chronic afebrile convulsions (epilepsy). Of the 201 in Group B, only six (3 per cent) have developed epilepsy.

Livingston concluded, as I had, that the patients in Group A had idiopathic epilepsy and that the fever acted as a trigger mechanism in the precipitation of the initial seizure. Those patients were treated with regular anticonvulsant medication. Patients in Group B had "simple febrile convulsions" and were not treated. This is a radical change in interpretation from the findings and conclusions reported by Livingston and associates in 1947,[3] and it now accentuates the importance of febrile convulsions and their significance in the convulsive disorders. It coincides with my previous emphasis on the serious prognosis of febrile convulsions.[4] Of course, Livingston's criteria for the inclusion of cases in Group A automatically select the cases of idiopathic epilepsy. The family physician who sees most of the

This study was supported by grants from Lederle Laboratories (American Cyanamid Company), Pearl River, N. Y., and Abbott Laboratories, North Chicago, Ill.

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initial fever convulsions will do well to consider this symptom one of the most serious in childhood. Attention is again directed to the significance of the sequence of events in "febrile convulsions." The fever precedes and rapidly precipitates the convulsion, and usually in the child under 3 years of age. In the infectious diseases, septicemia, and invasion of the central nervous system, the convulsion usually precedes or accompanies the rise in temperature, and at any age.

The history of febrile convulsions was adequately reviewed in my previous paper.[1] It has been well summarized and elaborated by Shanks in his recent papers.[6] He has aptly summarized the problem in his most recent report in which he stated: "The nature and significance of the isolated convulsion at the onset of an acute infection is of vital importance to our correct management of convulsions in childhood because upon this depends, by corollary, its prognosis. Whatever one's view of the nature of convulsions, whether or not one believes them all to be epileptic, it is certain that some children have one convulsion or a short burst of convulsions and thereafter have no more; others have recurrences, possibly not for many years after, and may ultimately require anticonvulsive treatment for the remainder of their lives. Some children have convulsions associated with severe disease of the central nervous system which may, as in meningitis, require urgent specific treatment; others show no demonstrable lesions, even at examination post mortem. The differentiation between these is essential to their proper management, and this will be considered in more detail."

Shanks found that only 12 per cent of "infantile convulsions" were followed by recurrence. However, 50 per cent of his patients with convulsions showed an abnormal electroencephalogram in adult life. The convulsions which occurred in the first year of life were the most benign. Shanks' statement that: "It is fortunately still possible to reach a reliable diagnosis and achieve adequate treatment without the aid of such specialized knowledge and equipment as electroencephalography entails" is quite true but, nevertheless, electroencephalography has provided us with more information in the study of the convulsive state than any aid we have ever had.

Whether a child has one or a series of convulsions and whether these are incited or produced by fever or infection, the electrogram will usually furnish objective evidence of the greatest value in diagnosis, prognosis, and evaluation of treatment. In a study of the siblings and relatives it is of inestimable value in establishing the hereditary origin of the convulsive state.

TABLE I

| AGE FIRST SEIZURE | CASES |
|---|---|
| Under 1 yr. | 73 |
| 1-2 yr. | 102 |
| 2-3 yr. | 50 |
| 3-5 yr. | 40 |
| 5-8 yr. | 32 |
| No record | 5 |
| Total | 302 |

## PRESENT SERIES

In the present series of 302 children with febrile convulsions, 226 (or 75 per cent) occurred in the first three years of life, and all occurred before 10 years of age (Table I). Eighty-six (29 per cent) of this series of cases

had only one seizure; however, nineteen (22 per cent) of these eighty-six patients gave a positive family history of convulsions, and four of these nineteen patients had positive electrograms. This would indicate that most children who have only one convulsion have, nevertheless, an inherited potential epilepsy and that more convulsions may be anticipated. Possibly they have occurred and have not been recognized or reported. In those known to have recurrences the free interval has been as long as thirteen years. Only twenty-two of these eighty-six patients had the single seizure in the first year of life.

TABLE II

| FAMILY HISTORY | CASES |
|---|---|
| Siblings affected | 21 |
| Parents affected: | |
| One | 32 |
| Both | 1 |
| Uncles, aunts, grandparents, cousins | 90 |
| Apparently negative | 155 |
| No record | 13 |
| Total (relatives affected) | 144 |
| (48 per cent cases with positive family histories) | |

TABLE III

| BIRTH HISTORY | CASES |
|---|---|
| Normal | 201 |
| Abnormal* | 56 |
| Cesarean section | 12 |
| Premature | 6 |
| No record | 27 |
| Total | 302 |

*Diseases in pregnancy, prolonged labor, forceps, etc.

In previous reports I have designated the age period between 6 months and 3 years as the convulsive age of childhood.[1] Forty-seven per cent of all convulsions of childhood occur within this thirty-month period. Fourteen per cent of my patients with epilepsy give a history of previous "infantile convulsions," usually before 3 years of age. Most of these were febrile convulsions; however, the true onset, at least of the final phase of epilepsy, occurs in the majority of cases between 3 and 10 years of life.

It seems that the more thoroughly one is able to delve into the family history, the higher is the incidence of convulsions found. In this series over half of the families were apparently negative (Table II). The birth history was normal in 201 patients (Table III). There were 162 boys and 140 girls.

Electroencephalograms were done on 180 patients. Of these, 133 (or 74 per cent) were positive. The findings included the typical cerebral dysrhythmia of petit mal or of grand mal epilepsy, the scattered spikes of brain injury residue, and the slow waves of chronic encephalitis.

TABLE IV

| DIAGNOSIS (FINAL) | CASES |
|---|---|
| Idiopathic epilepsy | 66 |
| Cerebral birth injury residual, convulsions | 35 |
| Convulsions | 146 |
| Encephalitis with convulsions | 17 |
| Brain hemorrhage residual with convulsions | 8 |
| Cerebral dysgenesis | 5 |
| Cerebral anoxia | 2 |
| Rheumatic fever | 2 |
| Miscellaneous | 21 |
| Total | 302 |

In many cases the positive electrograms helped to make or to confirm a diagnosis. All of these cases were first designated as "fever convulsions." Many were so dismissed by the family physician. A careful history, a complete examination, laboratory studies, and electrograms made it possible to replace a symptomatic pseudonym with an established diagnosis. Time and subsequent developments, especially

recurrence of seizures, have provided additional information with opportunity for revision of diagnosis.

The final diagnoses reveal that most "febrile convulsions" have an organic basis (Table IV). In 48 per cent of the cases a definite diagnosis is not possible at this time, but even in these, thirty-four (71 per cent) of the forty-eight electrograms which were done show positive findings. One hundred patients started with febrile convulsions and continued to have recurring convulsions without fever.

## DISCUSSION

A febrile convulsion, as defined above, is a symptom of an organic cerebral lesion precipitated by an elevated body temperature. An immediate investigation should always be made when this symptom is precipitated. It does not occur in a normal child. It does occur in about 2 per cent of sick children. A fever of any origin so accelerates the metabolism that it precipitates or produces a convulsion in the individual with a low convulsive threshold which varies with each child. The family history is positive in almost half of the cases, indicating an hereditary trend which is of about the same order as in diabetes. The increasing number of studies of febrile and infantile convulsions attests to the gravity of the problem and a gradual appreciation of its relationship to epilepsy. The electroencephalograph has provided the means to make an objective study of patients with convulsive disorders.

Those who would minimize febrile and single convulsions in childhood must match the cases and the studies of Livingston,[2] Shanks,[6] Zellweger,[7] Peterman,[1] and others. The predominance of evidence in the largest series of cases followed personally for the longest periods of time indicates that the convulsive tendency is inherited and as a potential hazard. It indicates that every convulsion is the most serious symptom in childhood and deserves careful investigation.

This study has been made to find answers to the questions which arise whenever a child has a convulsion.

What is the cause? A diagnosis is possible in 52 per cent of the cases if the study is complete with electroencephalography.

What is the treatment? When possible, this should be specific rather than symptomatic. The plan of immediate therapy is outlined in Table V.

TABLE V. IMMEDIATE TREATMENT

| |
|---|
| 1. Sodium phenobarbital, subcutaneously, intramuscularly, or intravenously, every six hours until desired effect. |
| 2. Magnesium sulfate, by mouth or by rectum, in 50 per cent solution; intramuscularly in 25 to 50 per cent solution, or intravenously, *slowly*, in 20 to 25 per cent solution. |
| 3. Paraldehyde, by mouth, by rectum, intramuscularly, or intravenously. |
| 4. Chloral hydrate by mouth or by rectum. |
| 5. Chloroform or vinyl ether by inhalation. |
| 6. Oxygen, when convulsion prolonged. |
| 7. Tribromoethanol (Avertin) by rectum. |
| 8. Spinal fluid drainage and air replacement. |

Will there be a recurrence—and when? Twenty-nine per cent of these patients had only one convulsion. Fifty-seven per cent of those had positive electrograms, indicating that a second convulsion was potentially possible at any time.

(Seventy-four per cent of all the patients in this series had abnormal electrograms but a definite diagnosis or interpretation is not possible, as yet, in 22 per cent of these.)

## CONCLUSION

Febrile convulsions usually occur in the first three years of life in children with an inherited convulsive tendency. Every convulsion is a major symptom with a 71 per cent probability of recurrence. In 74 per cent of the children with febrile convulsions the electrogram reveals evidence suggesting an organic brain lesion. Thorough study will reveal the basic cause or diagnosis in 52 per cent of the cases.

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# AN EVALUATION OF THE CURD-FORMING PROPERTIES OF MILK MIXTURES USED IN INFANT AND CHILD FEEDING

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THE adaptation of cow's milk as a dependable substitute for breast milk owes its successful achievement to a series of modification processes which were evolved gradually and more or less simultaneously within the past half century. These processes modify cow's milk in order to render it satisfactory for infant feeding with respect to safety, digestibility, and nutritional balance.

The modifications introduce into cow's milk one of four types of change: (a) destruction of pathogenic bacteria, (b) abolition of "hard-curd" properties, (c) adjustment of the relative proportion of carbohydrate, and (d) dilution with water. The changes represented by steps *c* and *d* are of lesser importance, for a number of feeding studies are on record in which infants have been fed satisfactorily on cow's milk without carbohydrate addition or appreciable dilution.[1, 2] Protection against contaminating bacteria and the elimination of large, firm coagula are essential for continued success in artificial feeding.

Abolition of the "hard-curd" properties, which will be discussed here, was first emphasized by Brennemann[3] in 1913 and was quickly adopted by all successful systems of artificial feeding. But it was not possible until fairly recently to subject the curd-forming properties of cow's milk and its numberless modifications to estimation by quantitative investigative methods. The development of the curd tension and curd number techniques have made this feasible.[4, 5]

The present report is a summary of observations made intermittently over a period of years on the coagulation behavior of various cow's milk feeding mixtures. These milk preparations have been studied with the aid of the curd tension test and the curd number test. The curd tension test measures the resistance to the passage of a wheel-shaped "knife" through clotted milk or a milk mixture which has been made to coagulate in a beaker under standardized circumstances. The resistance of the clot or curd is measured on a scale calibrated in terms of grams. The lower the reading the softer the curd. All determinations are made simultaneously in duplicate, and the mean taken as the definitive reading.

One set of curd tension tests in this study was carried out with the "standard" coagulant mixture recommended by the Special Committee of the American Dairy Science Association (10 ml. of a 0.45 per cent pepsin solution in 0.1 N hydrochloric acid per 100 ml. of milk) but the determinations themselves were carried out at 37° and 40° C. rather than at the suggested 35° C. Inasmuch as this coagulant fluid is much unlike that secreted by the infant stomach, additional tests were carried out simultaneously with a coagulant fluid

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TABLE I. COAGULATION BEHAVIOR OF DIFFERENT FORMS OF MODIFIED MILK (MEAN VALUES)

| | MILK | MODIFICATION | AVERAGE CURD "STANDARD" COAGULANT | | TENSION (GM.) "PHYSIOLOGIC" COAGULANT | | AVERAGE CURD NO. | | NO. OF MILK SPECIMENS |
|---|---|---|---|---|---|---|---|---|---|
| | | | 37° | 40° | 37° | 40° | 37° | 40° | |
| Exp. 1 | Pasteurized | No modification | 49 | 62 | 77 | 71 | 139 | 135 | 22 |
| | Pasteurized | Heated to boiling | 4 | 6 | 7 | 9 | 204 | 184 | 3 |
| | Pasteurized | Boiled 5 minutes | 6 | 7 | 8 | 10 | 204 | 180 | 2 |
| Exp. 2 | Pasteurized | No modification | 55 | 62 | 58 | 64 | 130 | 127 | 2 |
| | Pasteurized | Diluted 5% | 55 | 61 | 57 | 63 | 135 | 130 | 1 |
| | Pasteurized | Diluted 10% | 31 | 34 | 52 | 55 | 150 | 146 | 5 |
| | Pasteurized | Diluted 15% | 30 | 32 | 34 | 39 | 154 | 150 | 1 |
| | Pasteurized | Diluted 20% | 27 | 39 | 41 | 40 | 157 | 156 | 8 |
| | Pasteurized | Diluted 30% | 25 | 27 | 24 | 21 | 170 | 188 | 7 |
| | Pasteurized | Diluted 35% | 12 | 14 | 13 | 14 | 171 | 170 | 2 |
| | Pasteurized | Diluted 40% | 6 | 7 | 7 | 8 | 185 | 182 | 6 |
| | Pasteurized | Diluted 50% | 5 | 6 | 5 | 6 | 209 | 208 | 6 |
| | Pasteurized | Diluted 60% | 1 | 2 | 2 | 3 | 244 | 239 | 2 |
| Exp. 3 | Pasteurized | No modification | 51 | 63 | 55 | 65 | 135 | 130 | 2 |
| | Pasteurized | Lactic acid | 10 | 12 | 13 | 15 | 219 | 201 | 13 |
| | Pasteurized | Mashed banana 5% | 42 | 60 | 45 | 64 | 155 | 148 | 3 |
| | Pasteurized | Mashed banana 10% | 25 | 39 | 30 | 33 | 194 | 168 | 1 |
| | Pasteurized | Mashed banana 20% | 16 | 17 | 18 | 19 | 208 | 206 | 1 |
| | Pasteurized | Rennet | 15 | 16 | 17 | 19 | 196 | 204 | 2 |
| Exp. 4 | Pasteurized | No modification | 45 | 52 | 50 | 55 | 145 | 140 | 2 |
| | Pasteurized | Limewater | 44 | 55 | 51 | 56 | 133 | 131 | 6 |
| Exp. 5 | Pasteurized | No modification | 43 | 55 | 66 | 68 | 132 | 131 | 2 |
| | Pasteurized | Apple syrup 1 oz. per pt. | 39 | 51 | 61 | 63 | 146 | 147 | 2 |
| Exp. 6 | Homogenized | No modification | 13 | 15 | 16 | 17 | 215 | 201 | 6 |
| | Homogenized | Heated to boiling | 10 | 15 | 14 | 15 | 233 | 232 | 4 |
| | Homogenized | Boiled 5 minutes | 10 | 11 | 14 | 15 | 225 | 233 | 2 |
| Exp. 7 | Raw | No modification | 54 | 65 | 75 | 95 | 112 | 116 | 6 |
| | Raw | Heated to boiling | 4 | 7 | 12 | 12 | 211 | 201 | 5 |
| | Raw | Boiled 5 minutes | 4 | 8 | 10 | 13 | 215 | 197 | 2 |
| | Raw | Diluted 30% | 25 | 28 | 32 | 26 | 121 | 147 | 1 |
| | Raw | Diluted 35% | 19 | 22 | 12 | 4 | | | 1 |
| | Raw | Diluted 40% | 17 | 17 | 5 | 2 | 162 | 201 | 1 |
| Exp. 8 | Raw goat | No modification | 33 | | | | 148 | | 1 |
| Exp. 9 | Pasteurized goat | No modification | 20 | 24 | | | 132 | 135 | 2 |
| Exp. 10 | Evaporated | No modification | 0 | 0 | 0 | 0 | 290 | 280 | 1 |
| Exp. 11 | Chocolate | No modification | 1 | 3 | 5 | 6 | 239 | 230 | 2 |
| Exp. 12 | Pasteurized | No modification* | 45 | 46 | 47 | 48 | 127 | 120 | 2 |
| | Dexin | Dexin 5% | 43 | 45 | 44 | 46 | 126 | 122 | 5 |
| Exp. 13 | Pasteurized | No modification* | 35 | 38 | 36 | 42 | 146 | 139 | 2 |
| | Enzylac added pancreatic enzyme | | 34 | 38 | 36 | 41 | 145 | 140 | 9 |
| Exp. 14 | Concentrated | | | | | | | | |

*Control samples from same batch.

which reproduces more closely the "physiologic" response of the infant stomach[6] (3 ml. of a 0.6 pepsin solution mixed with 2.3 ml. of N hydrochloric acid per 100 ml. of milk). It must be remembered that great variations occur both in the casein content and physical characteristics of cow's milk, and in the motor and secretory response of the stomach to it.

The curd number test describes in numerical units the size pattern of the curds which form when milk or a milk mixture is made to coagulate within agitated rubber bags suspended in a water bath after addition of a standardized coagulating mixture. The curds which form are hardened in a formalin solution and then graded according to size by passage through sieves. The fractions thus secured are weighed, and the weights incorporated into a formula which makes it possible to compare on a percentage distribution basis one form of milk with another. The results are expressed on an abitrary "curd number" scale which runs from *100* to *300*. The number *100* thus derived represents only large curds, whereas, number *300* represents innumerable small curds. The higher the number, the smaller the curds.

The curd number tests in this study were performed in triplicate within mechanically agitated rubber bags at both 37° and 40° C., employing the same "physiologic" coagulant solution described for the curd tension test. With each batch of modified milk undergoing test one or more batches of plain pasteurized milk from the same source were run through at the same time, for control purposes.

Exp. 14 Concentrated creatic enzyme
*Control samples from same batch.

## RESULTS

*Effect of Heat.*—Table I summarizes typical observations. It can be seen that unmodified pasteurized milk tends to be slightly less "hard-curd" than completely unprocessed raw milk. All specimens of milk tested had been pasteurized by the "holding" method (63° C. for 30 minutes). This slight reduction as the result of pasteurizing temperature confirms the results of an earlier study.[2]

Additional studies of the influence of heat upon milk are recorded in the observations made when milks were exposed to progressively higher temperatures over increasing intervals of time (Fig. 1). All heating was done in a vessel provided with a reflux condenser to eliminate errors due to evaporation. Each curve represents the mean of five experiments, all done with the same batch of milk. At the temperature used in the "holding" method of pasteurization, 63° C. (143° F.), little effect was noted even after 30 minutes. At 71° C. (160° F.), which is "flash" pasteurizing temperature, the effect was also almost negligible until many minutes had passed. At the temperature often used in Europe for pasteurization, 80° C. (176° F.) the effect was greater and increased progressively with the passing of time, At 5 mintues the curd number was 204 and the curd tension was 17 Gm., or just on the border of what has been defined as soft-curd milk on the basis of another investigation.[5] At 30 minutes the curd number was 212, and the curd tension 4 Gm. When the milk was raised to 100° C. (212° F.), it became soft curd immediately, with a curd tension of 3 Gm. and a curd number of

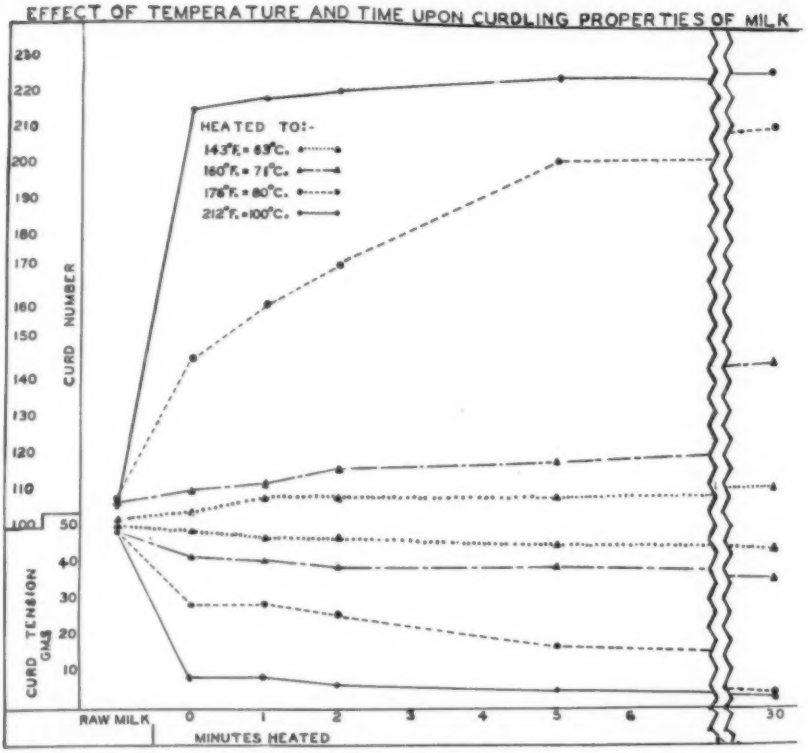


Fig. 1.—The effect of heating, in various times up to 30 minutes, on the curdling properties of milk is shown. Normal pasteurization has very little effect; heating to 160°F. (71°C.) produces slightly higher curd numbers and lower curd tensions. Heating to 80°C. (used to a great extent in Europe) gives a pronounced effect, and heating to boiling temperatures produces a soft-curd milk which is not changed much by prolonged heating. High curd numbers mean small curds, corresponding to low curd tensions. A "soft-curd milk" has a curd number of 200 or over, and a curd tension of 15 Gm. or less.

TABLE II. EFFECTS OF MODIFICATIONS UPON CURD FORMATION OF COW'S MILK

| | | |
|---|---|---|
| a. | No effect | Lime water; dilution with water in less than 10% amounts; addition of corn starch derivatives; addition of fresh banana in less than 5% amounts. |
| b. | Slight effect | Addition of apple syrup; Enzylac treatment; addition of 5 to 10% of fresh banana; dilution with water in 10 to 30% amounts. |
| c. | Marked effect (soft-curd milks) | Boiled milk; homogenized milk; lactic acid milk; commercial chocolate milk; rennet-treated milk; banana milk (addition of 20% fresh banana and over); marked dilution (adding 35% or more water); "evaporation"; rennet custards; buttermilk; acidophilus and other curdled sour milks. Powdered milks. |

216 (Fig. 1), well in the soft-curd range. Further boiling induced little additional change even after 30 minutes.

In nearly every experiment the readings secured with the curd tension meter were considerably higher with the "modified" hydrochloric curd tension procedure recommended by the American Dairy Science Association is strictly applicable to studies of human digestion.* Comparison of the determinations at 37° and 40° C. indicates that the higher temperature of fever tends in general to produce tougher and larger curds than

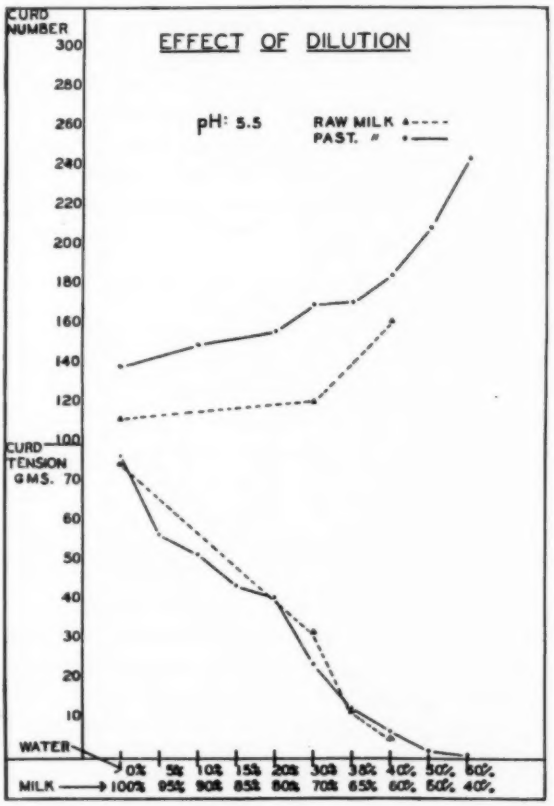


Fig 2.—Effect of dilution on curdling properties of milk shows a somewhat greater effect on pasteurized than on raw milk. The milk does not get into the range of "soft-curd milks" until the dilution is about 50 per cent water to 50 per cent milk.

acid-pepsin coagulant (simulating the natural conditions in the stomach) than with the "standard" test solution. The curds were also larger. This raises the question of whether the those which form at normal body temperatures. This difference is much more prominent with "hard-

*For control of milk processing this somewhat arbitrary method has been found satisfactory for differentiating between "hard-curd" and "soft-curd" milk.[4]

curd'' than ''soft-curd'' milks. Other modifications, addition of lactic acid, and precoagulation with rennet also diminish the curd tension and curd size (Table II) to the zone of ''soft-curd'' milk.[5] Lime water has little if any influence. Addition of apple syrup gives a reduction of about 10 per cent. Carbohydrate modifiers derived by hydrolysis of corn starch have a hardly noticeable effect. Step-by-step dilution with water causes a progressive decrease in curd tension and size, but the soft-curd limit is not passed until the dilution has reached 35 per cent water added to milk (Fig. 2).

Addition of mashed fresh banana also reduces the curds, and the soft-curd range is attained by a 20 per cent mixture. Enzylac seems little different from ordinary pasteurized milk. Evaporated milk, which is first homogenized and then autoclaved in the can, forms fine curds.

A recently introduced milk product on the market is concentrated milk. In order to make ordinary milk from this, two volumes of water should be added to one volume of concentrated milk. Concentrated milk, which in addition to being concentrated has also been pasteurized and homogenized, shows low curd tension and fine curds after reconstitution.

*Goat's Milk.*—Many goat milk dairymen believe that goat's milk is more ''soft-curd'' than cow's milk. To check this hypothesis, a large number of goat milk specimens from different breeds were secured for testing from a farm in the Philadelphia milk shed. The tests were done between September, 1949, and May, 1950. The results are summarized in Table III. It will be noted that raw goat's milk exhibits wide variability with respect to curd tension and curd number, just as does cow's milk. There is also the similar phenomenon of differences among breeds, the Nubian giving milk with the hardest and largest curds, and the Toggenburg the softest and smallest curds. In the past we have had some specimens of raw goat's milk which exhibited curd tension readings of about 50 Gm., and correspondingly low curd numbers. The raw and pasteurized goat's milk specimens tested were less hard curd than the similar forms of cow's milk, but still far from the soft curd zone. The homogenized goat milk specimens were clearly soft curd.

The degree of parallelism between curd tension and curd number is not

TABLE III. CURD TENSION AND CURD NUMBER VALUES FOR GOAT'S MILK FROM A FARM IN THE PHILADELPHIA AREA

| | NO. OF SPECIMENS | CURD TENSION (GM.) | | NO. OF SPECIMENS | CURD NUMBER | |
|---|---|---|---|---|---|---|
| | | MEAN | RANGE | | MEAN | RANGE |
| a. Raw goat's milk | | | | | | |
| Alpine | 17 | 31.2 | 18-55 | 9 | 120 | 106-135 |
| Nubian | 16 | 39.5 | 35-50 | 8 | 107 | 101-121 |
| Toggenburg | 16 | 23.9 | 15-45 | 9 | 137 | 105-194 |
| Saanen | 16 | 32.8 | 22-60 | 9 | 118 | 101-132 |
| b. Mixed pasteurized* | 35 | 24.2 | 10-42 | 16 | 128 | 101-202 |
| c. Homogenized pasteurized* | 7 | 5.7 | 4-10 | 6 | 220 | 196-229 |

*Pooled samples of milk from all four named breeds as sold commercially.

precisely the same with goat's milk as with cow's milk. Comparison of the mean values given in Table III for goat's milk and Table IV for cow's milk shows that a mean curd number of 220 corresponds to a mean curd tension of 5.7 Gm. for goat's milk, but to a mean curd tension of 11 to 12 Gm. for cow's milk. In other words, goat's milk of a given curd tension forms larger curds than cow's milk of the same curd tension. This difference is no doubt referable to some protein component more tenacious in goat's milk than in cow's milk. Goat's milk has a slightly higher globulin and albumin content and slightly lower casein content than cow's milk.

An experiment designed to test the effect of heat upon the curd-forming behavior of goat's milk was made and the data are shown in Table V.

*Homogenized Cow's Milk.*—Of special interest is market homogenized milk, which was submitted to continuous investigation from 1940 through 1946. Homogenization effectively converts hard-curd to soft-curd milk, as has been noted many times.[4, 5] The averages of curd number and curd test figures for homogenized milk from six of the leading dairies in Philadelphia, representing a total of approximately 1,500 samples over a six-year period, are tabulated in Table IV.

TABLE IV. CURD TENSION AND CURD NUMBER OF HOMOGENIZED MILK FROM SIX PHILADELPHIA DAIRIES: MEAN VALUES FOR A SIX-YEAR PERIOD (1940 TO 1946)

| | JAN. | FEB. | MAR. | APR. | MAY | JUNE |
|---|---|---|---|---|---|---|
| Curd tension (Gm.) | 12 | 10 | 9 | 9 | 8 | 8 |
| Curd number | 220 | 228 | 228 | 226 | 232 | 240 |

| | JULY | AUG. | SEPT. | OCT. | NOV. | DEC. |
|---|---|---|---|---|---|---|
| Curd tension | 8 | 7 | 11 | 15 | 14 | 12 |
| Curd number | 235 | 251 | 220 | 203 | 210 | 209 |

It will be noted that a slight seasonal fluctuational takes place. The variations among the individual dairies were of somewhat greater magnitude.

TABLE V

| | CURD TENSION (STANDARD TEST) (350° C.) | CURD NUMBER (37° C.) |
|---|---|---|
| Pasteurized pooled goat's milk | 20 Gm. | 165 |
| Same milk brought to boiling temperature | 6.0 | 220 |
| Same milk boiled for 3 minutes | 2.0 | |
| Same milk boiled for 5 minutes | 2.0 | |

## SUMMARY

The curd-forming properties of milks and milk mixtures used in infant feeding have been studied, employing testing procedures which simulate intragastric conditions. The results confirm that heat treatment, dilution with water acidification and homogenization, if adequately employed, are effective methods of eliminating the tendency of unmodified cow's milk to form large firm coagula in the stomach of the infant and child. Fever temperatures aggravate the tendency to "hard formation." Apple syrup reduces this tendency a little; banana, more so; whereas corn starch derivatives exert no influence.

Goat's milk is not as often maintained, naturally soft curd but shows similar reaction as cow's milk toward treatment with heat, dilution, and homogenization.

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# PERSISTENT SEQUELAE OF BULBAR POLIOMYELITIS

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THE prognosis for recovery from disability in patients surviving acute poliomyelitis with cranial nerve involvement has generally been considered good.[1-5] This impression was not confirmed in subsequent observation of patients who had poliomyelitis in the Minnesota epidemic of 1946. Accordingly, as a preliminary survey, a series of fifty patients were reviewed seventeen to nineteen months after their episode of acute bulbar poliomyelitis.† This survey has shown that a majority of these patients have continued to have residual impairment.

## PATIENT MATERIAL AND OBSERVATIONS

A series of fifty patients who survived acute bulbar poliomyelitis were recalled seventeen to nineteen months after their acute illness to obtain interval histories and repeated physical examinations. The acute illness of all of these patients had occurred during the 1946 poliomyelitis epidemic in Minnesota, and all had at that time been hospitalized at the Minneapolis General Hospital. In a review of hospital charts, these patients were selected upon the basis of their noted cranial nerve involvement, in association with little or no evident spinal involvement. Selection was otherwise random among the patients having this pattern of illness.

During their acute illness, these patients were observed to have a variety of cranial nerve motor impairments, the most common of which was weakness of the pharyngeal musculature, with impairment of the muscles of the face, of mastication, and of the tongue occurring in diminishing incidence. Their age at onset of their illness varied from 1½ to 38 years. Thirty-four (68 per cent) of the patients were less than 17 years of age. Their hospital stay varied from one to eight weeks. Tracheotomy was performed in none of these patients.

In this inquiry, twenty-nine patients were seen fifteen months after onset of their acute poliomyelitis. Nineteen were seen sixteen months, and two were seen seventeen months after their acute illness. It was found that forty-four of these patients continued to have persistent or recurrent symptoms of cranial nerve involvement and thirty-six had corresponding demonstrable physical findings.

In these patients, the pharynx was the most common site of disability (Fig. 1). The most troublesome symptoms were those occurring incident to swallowing solid foods. Forty-seven of these patients had this difficulty in the period of acute illness and twenty-eight had persistent or recurrent difficulty at the time of this inquiry. The patients reported a necessity for chew-

This study was supported by the Hubert Humphrey Fund and the National Foundation for Infantile Paralysis, Inc. It was conducted at the Minneapolis General Hospital.

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†The term "bulbar poliomyelitis" is here used in its most general definition as referring to that form of this disease in which there is involvement of cranial motor nerves.

ing food very completely and swallowing it slowly and in small amounts. Some had become accustomed to "washing down" their food with liberal amounts of fluid. In spite of this learned caution, they continued to have variable degrees of difficulty, such as choking, gagging, gulping, and regurgitation.

Forty of these patients had difficulty in swallowing liquids during their acute illness and eleven of these had been unable to swallow liquids for periods of from one to seven days. Nasal regurgitation of liquids occurred in thirty-three of these patients during their acute illness and this continued to be a troublesome problem in sixteen of them at the time of the follow-up examination (Fig. 2). This difficulty was manifest in these patients particularly when bending forward, as when drinking at a fountain. There was little correlation between incidence of difficulty in swallowing solids and that of nasal regurgitation.

A "nasal" quality of voice was observed frequently in this group. It was noted in twenty-five of the patients during their acute illness and in sixteen at the time of their follow-up examination.

At the occasion of the follow-up visit the act of swallowing and the speech were observed in these patients. The greater than normal effort required in swallowing was indicated commonly by an associated forward thrusting of the head, which was in some instances combined with turning or tilting of the head to one side. On gross inspection of the pharynx significant changes in the contour of the posterior and lateral wall was noted in two patients. In these patients both a medialward displacement of the lateral wall and an anterior displacement of the posterior wall were seen on one side. Distinct

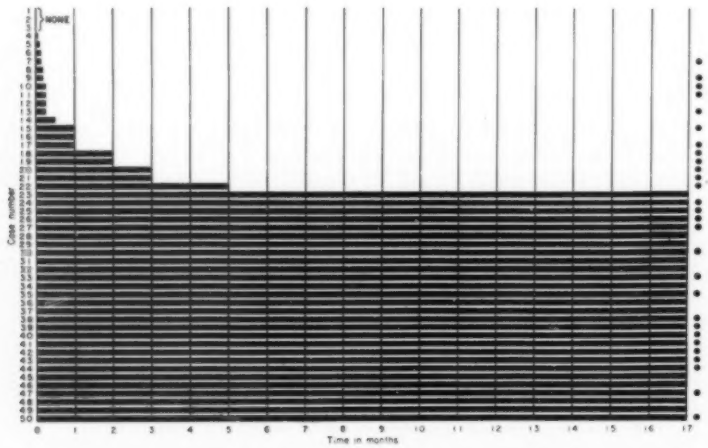


Fig. 1.—Duration of difficulty in swallowing solids. The duration of difficulty is indicated by the horizontal bars. The observation of abnormality of the palate in these patients is indicated by the dots in the right-hand margin. Patients are numbered empirically in the left-hand column. The patients identified by number in this figure bear these same numbers in subsequent figures.

paralysis of the palate was observed in twenty-five (56 per cent) of the patients. This paralysis was manifested incident to phonation by an asymmetry of elevation of the soft palate, by lateralward deviation of the palate, or by a combination of these abnormal motions. Paralysis of the palate was observed in sixteen of the twenty-eight patients who continued to have difficulty in swallowing solids. It was also present in all sixteen patients having nasal regurgitation of liquids and in thirteen of the sixteen patients who continued to have nasal voice.

Paralysis of the palate was present in three patients who had no residual impairment of swallowing and no nasal speech at the time of follow-up examination. Conversely, eleven of the patients having recurrent difficulty in swallowing solids had no visible paralysis of the soft palate. This disparity of function of the pharynx and distinguishable paralysis of the soft palate are indicated in Fig. 1, in which this paralysis is indicated by a symbol.

An incidental observation was that the gag reflex was diminished or absent unilaterally or bilaterally in a few of these patients having residual impairment. Impairment of function of the larynx during the acute stages of poliomyelitis was found difficult to evaluate. None of the patients of this series were obviously aphonic. On inquiry at the time of the follow-up examination, ten patients reported persistent hoarseness or a lowering of pitch of the voice, which was manifested particularly in singing. Indirect laryngoscopy was performed in thirteen patients and unilateral vocal cord weakness was seen in three of these patients.* Additional persistent complaints which possibly indicated involvement of the larynx included poor volume of speech, frequent "clearing of the throat," and hacking cough. Choking spells, unassociated with eating or drinking, were reported in three patients.

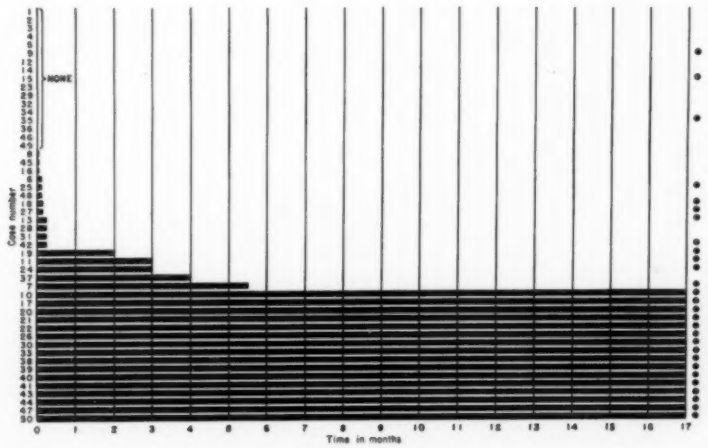


Fig. 2.—Duration of nasal regurgitation of liquids. (See legend for Fig. 1 for comment regarding symbols and patient numbers.)

*Laryngoscopy was performed by Drs. Robert Priest and Harold Ulvestad of the Department of Otolaryngology of the Minneapolis General Hospital.

A particular effort was made to discover a correlation of persistent bulbar sequelae with the incidence or complication of respiratory infections. No significant correlation could be found. The one exception was that of an adult woman who had extensive paralysis of the face, pharynx, and larynx during her acute poliomyelitis, which paralyses were evident in moderate or severe degree at the time of follow-up examination seventeen months later. This patient had suffered acute episodes of pneumonia in the fourth, eighth, eleventh, and twelfth months after her acute illness. The pneumonia was demonstrated roentgenologically in the first three of these episodes. Roentgenograms of the chest were obtained in all patients at the time of the follow-up examinations and all, including that of the exceptional patient mentioned above, gave no evidence or only questionable evidence of pulmonary pathology.*

Conversely, the occasional incidental illnesses which these patients experienced were occasions of exaggeration of their disability as manifested by greater dysphagia and diminished clarity of speech.

During the acute stage of poliomyelitis, impairment of function of the lower division of the facial nerve was present in 25 of the 50 patients in this series and ten patients had an associated impairment of its upper division. In 3 of these patients this paralysis was not associated with involvement of the pharynx or larynx. Fifteen months later a distinct impairment of function of the lower division of the facial nerve was found in seventeen patients. This was associated with impairment of function of the upper division in five patients (Fig. 3). Three patients were still unable to close one eye at the time of this examination.

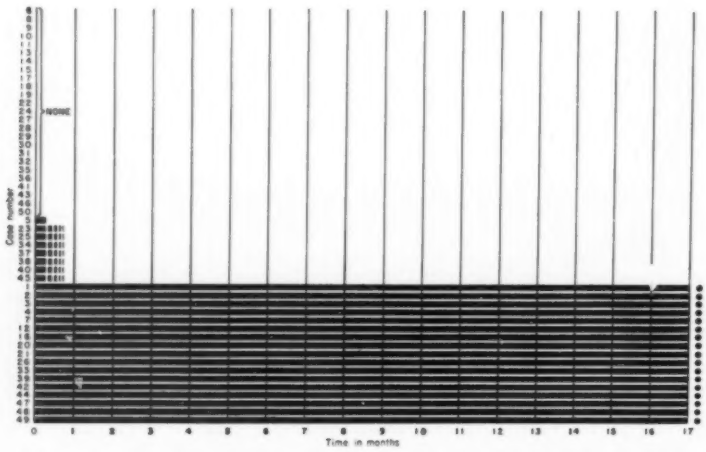


Fig. 3.—Duration of paralysis of face. Persistence of evidence of paralysis of face is indicated by horizontal bars and the dots in the right-hand margin.

Recovery in each of these categories of function occurred to a diminishing degree in successive periods of convalescence. Thus, fifteen of the patients

*The roentgenograms were evaluated by Dr. Oscar Lipschultz, Radiologist at the Minneapolis General Hospital, and by Dr. Herbert S. Stauffer of the Department of Radiology of the University Hospitals, Minneapolis.

who recovered from the "nasal quality" of voice reported that this recovery occurred within one month of the onset of the illness, and all twenty-nine patients who recovered from the impairment did so within eight months of their acute illness. In the remainder of the observation period, those patients with persisting difficulty noted no conclusive evidence of improvement. Those patients whose disability was intermittent continued to have symptoms of this disability at their usual incidence and severity. It was noted generally that improvement in specific abilities continued longer and was greater in degree in the children (less than 17 years of age) than in the adults of this series.

The possible contribution of psychic factors to the impairments of function reported and observed was considered. Several of the patients admitted embarrassment which was appropriate to their impairment. Several described themselves or were described by relatives as being of a distinctly different temperament than before their acute poliomyelitis illness. This difference consisted usually of a greater degree of "nervousness," greater concern about usual problems, and a lesser tolerance of stress. No clear evidence of hypochondriasis was found and in no instance was their impairment obviously the expression of a neurosis. However, it was commonly observed that these forms of disability were aggravated by fatigue or excitement and, conversely, the disability was improved by rest.

## DISCUSSION

The unanticipated high incidence of persistent sequelae of bulbar poliomyelitis places our experiences with this disease entity in striking contrast with the experience of other observers. Wilson[1] states, "It should be recognized that there is almost 100 per cent recovery of the pharyngeal muscles if life can be preserved through the first week of the disease." This is in accord with the earlier experience of Durand,[2] of Shambough, Harrison, and Farrell,[3] and the more recent experience of Green.[4] Peabody, Draper, and Dochez[5] agree with this impression but mention a single patient in whom paralysis of the face and tongue persisted for an unspecified period of time.

Brahdy and Lenarsky[6] in 1933 studied 123 patients with cranial nerve lesions due to poliomyelitis. They found that swallowing difficulty was relieved in the majority of their patients within a week. However, they reported five patients who were unable to swallow for a period ranging from twenty-one to seventy-one days. These patients were later studied at intervals of three and one-half to six months from the onset of their acute illness, and at this time, these patients continued to have subjective complaints, such as an excess of saliva in the pharynx and a husky or nasal voice. One of these patients continued to have difficulty in swallowing. Four of the five patients had physical findings of residual cranial nerve weakness at the end of this observation period.

Significant comparisons may be made between the recovery of these cranial nerve innervations and the usual pattern of recovery of paralysis of spinal involvement. Thus, there is a relatively rapid recovery within the first few weeks of the acute disease. Thereafter the progress of recovery diminishes. Furthermore, the recovery is erratic and relatively unpatterned, much like that in polio-paresed limbs. The difficulties of deglutition and

speech behave also like other motor impairments in that they are accentuated incident to intercurrent illness, fatigue, or psychic disturbance.

The persistence of impairment noted would indicate that the involvement of the motor nuclei of the cranial nerves in acute poliomyelitis is of greater severity as well as of higher incidence compared to that noted in previous years.

SUMMARY

Residual neurological impairment has been reviewed in a series of fifty patients seventeen to nineteen months after their acute bulbar poliomyelitis. Unexpectedly, a high incidence of persistent disability has been found. At the time of this follow-up examination 88 per cent of the observation group continued to have symptoms of cranial nerve involvement. This involvement was demonstrated at physical examination in 72 per cent of this group. The schedule of recovery from these disabilities and the circumstances of their later examination are similar to those noted in patients having persisting motor impairment after "spinal paralytic" poliomyelitis.

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# PSEUDOMONAS INFECTIONS IN INFANTS AND CHILDREN

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THE human pathogenicity of *Bacillus pyocyaneus* and the character of the infections produced were delineated by Fraenkel's[1] classical description in 1917. The dermatosis produced by Pseudomonas is known to dermatologists as ecthyma gangraenosum and has been described in the American literature.[2] Hematogenous skin infections with *Pseudomonas aeruginosa* have also been described.[3] Although noma, or gangrenous stomatitis, was once common, especially in pest houses, the number of these cases produced by Pseudomonas cannot be accurately determined. Kerby,[4] in a critical review in 1947, accepted only thirty-nine cases of *Ps. aeruginosa* bacteremia in children. The following cases illustrate that infections from *Ps. aeruginosa* seem to have become more frequent following the widespread and indiscriminate use of antibiotics.

## CASE REPORTS

### *Noma*

CASE 1.—A 10-month-old white male was admitted on May 26, 1948, because of severe measles of two days' duration, accompanied by diarrhea. The patient had been given penicillin for five days before admission. *Shigella paradysenteriae* (Boyd 119) was isolated from the stool. Following the usual course the measles subsided, but because of a secondary pneumonia 100,000 units of penicillin were administered twice daily. On the tenth hospital day the patient developed a bilateral, ulcerating, purulent conjunctivitis with extreme swelling of both lids and sloughing of the lid margins. Similar lesions in the mouth and nose resulted in sloughing of the palate and nasal septum. *Ps. aeruginosa* was recovered in pure culture from these lesions. The erosion eventually spread to the skin surface around the mouth and nose. Despite special nursing care, the mouth was filled with thick, foul, greenish yellow pus most of the time. There was also marked recrudescence of the diarrhea, and Pseudomonas was the predominant organism on culture. The same organism was recovered from the blood and was found to grow in 5 units per milliliter of penicillin and 20 units per milliliter of streptomycin. Treatment consisted of supportive therapy, penicillin, streptomycin, and sulfadiazine. The infant became weaker, comatose, and expired on June 14, 1948. At autopsy, multiple small submucosal abscesses were found throughout the colon and on the surfaces of both lungs. Sections of these lesions were infiltrated with gram-negative organisms which were identified on culture as *Ps. aeruginosa*.

### *Pyoderma Gangrenosum*

CASE 2.—A 4-month-old Latin-American male infant was admitted to Brooke Army Hospital on April 17, 1951, because of recurrent diarrhea. On physical examination, the patient was found to be an extremely dehydrated acidotic infant of 10 pounds. No enteric pathogens were recovered on repeated stool examinations. Duo-

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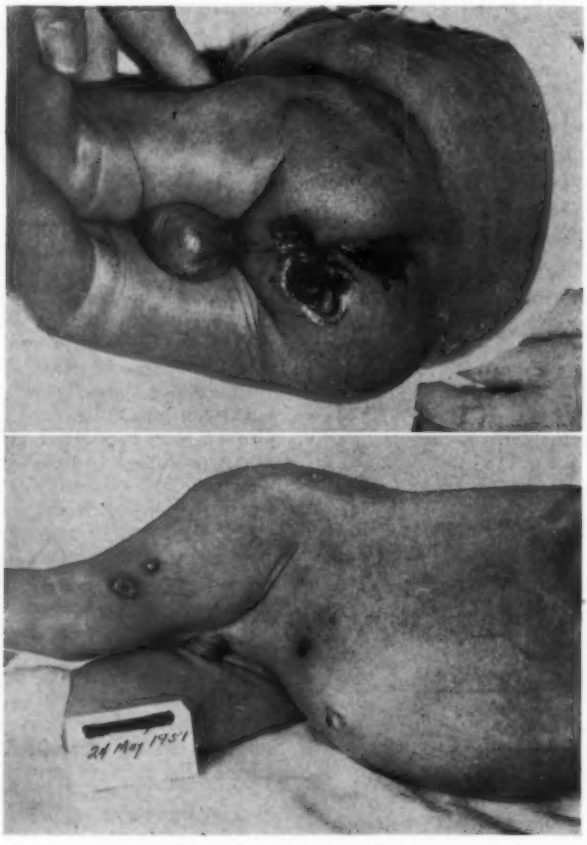
denal drainage revealed normal enzyme content. Diarrhea persisted in spite of vigorous therapy which included, in addition to appropriate parenteral fluids, penicillin 200,000 units twice daily. On May 17, 1951, penicillin was discontinued and chloramphenicol, 15 mg. per kilogram, was administered. Two days later, punched-out ulcers 1½ cm. in diameter appeared on the buttocks (Fig. 1). There was minimal reaction at the margins of these lesions. During the next four days they enlarged and became gangrenous. Similar lesions appeared over the entire body and the infant became jaundiced. On May 19 *Ps. aeruginosa*, not present in the stool on admission, became the dominant organism. The patient's temperature rose to 104° F. on May 24. The infant died May 26, 1951. Gram-negative rods were demonstrated in the microscopic sections from biopsy specimens of the lesions on the buttocks (Fig. 2). This organism was identified as *Ps. aeruginosa* and was the same organism as that recovered

*A.*




*B.*

Fig. 1 (Case 2).—*A*, *Pyoderma gangrenosum* on the fifth day. *B*, Metastatic lesions in *B. pyocyaneus* septicemia.

daily from the blood during the last five days of life. The organism was resistant to sulfadiazine, penicillin, streptomycin, aureomycin, chloramphenicol, terramycin, polymyxin, and bacitracin. An autopsy was performed four hours after death and pure culture of Pseudomonas was recovered from heart blood, spleen, skin lesions, and ulcers in the gastrointestinal tract.

*Septicemia*

CASE 3.—This premature 4 pound white female was delivered Dec. 13, 1948, by Cesarean section because of placenta previa. The cord, upon opening the uterus, was pulseless and the infant atonic and cyanotic. After re-

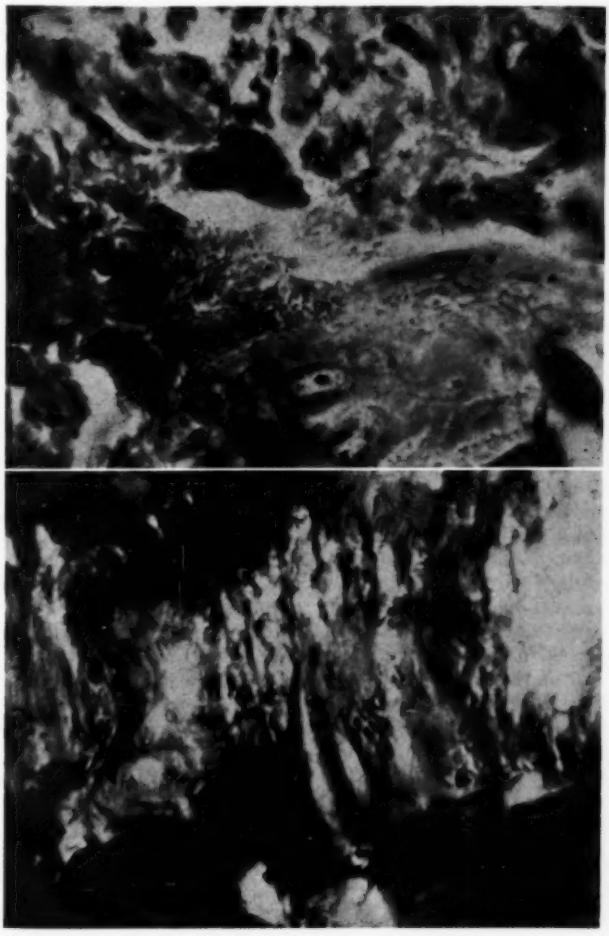



Fig. 2.—*A*, Cross section of an arteriole invaded by *B. pyocyaneus*. *B*, Tangential section of vessel wall invaded by *B. pyocyaneus*.*

*These microscopic sections were prepared by Mary Ferguson, M.T.

suscitation the infant seemed normal except for a forceps laceration behind the right ear. Prophylactic penicillin was administered in doses of 100,000 units twice daily. On the fifth day she refused feedings, became restless, and inflammation was noted around the laceration behind the right ear. This rapidly became hemorrhagic with a necrotic center. Cultures of this lesion were identified as *Ps. aeruginosa* and the same organism was isolated from the blood. Numerous maculopapular nodules were noted over the entire body, which became hemorrhagic and necrotic, forming ulcers with rolled edges. There was minimal reaction at the margin of these lesions. The patient developed scleredema on the eighth day. Therapy consisted of penicillin, streptomycin, sulfadiazine, and repeated blood transfusions. Scleredema subsided by the tenth day. No new abscesses developed, although a lesion behind the right ear and another on the mucocutaneous junction of the anus became black and necrotic. The liver was enlarged and contained several nodular masses. The organism recovered was reported to grow on 300 units per milliliter of penicillin, 100 units per milliliter of streptomycin, and 10 mg. per cent of sulfadiazine, but in vitro was inhibited by a combination of these three agents in the same concentrations. So long as all three were given, blood cultures were sterile and the patient steadily improved. Attempts to discontinue any of them singly, however, resulted in a return of bacteremia and fever. After thirty days of therapy all the lesions had disappeared and medication was discontinued. One year later, the patient was normal except for a severe cicatrix closing the right nostril.

### *Diarrhea*

CASE 4.—This one-year-old white female was admitted to Brooke Army Hospital on June 18, 1947, with a chief complaint of diarrhea of two months' duration. She had been hospitalized elsewhere on several different occasions and had been in the referring hospital for two weeks prior to transfer. Penicillin, 100,000 units three times daily, had been administered throughout this hospitalization. *Ps. aeruginosa* was the predominant organism in stool cultures. The patient was severely marasmic, dehydrated, and appeared both acutely and chronically ill. There were no localized physical findings of importance. Temperature persisted at 101° F. She had sixteen to twenty foul-smelling, soapy, green stools a day. Continuous intravenous infusions of glucose, blood, electrolytes, vitamin C, thiamine, and Solu-B were maintained. Wasting continued and the patient expired on the fourth hospital day. At autopsy, the significant findings were limited to the abdomen. There were many ulcers, 1 cm. in diameter, with rolled borders and undermined edges in the terminal 36 inches of the ileum and cecum and the proximal 12 inches of the colon. There was little reaction around these lesions and they resembled exactly those seen in pyoderma gangrenosum due to *Ps. aeruginosa*. Gram-negative rods were infiltrated throughout the margins of these ulcers and *Ps. aeruginosa* was identified in pure culture from these lesions. The wall of the ileum was markedly thickened to four times the average thickness, and microscopic examination demonstrated many gas bubbles in a large gas-filled space between the mucosa and the muscular wall. Pathological diagnosis was pneumatosis cystoides intestinalis.

### *Acute Upper Respiratory Tract Infection*

CASE 5.—A 7-week-old white male was transferred to Brooke Army Hospital Feb. 3, 1951, for plastic repair of a congenital harelip and cleft palate. Weight was 8 pounds 5 ounces, and length, 20 inches. On physical examination, the child was found to have a purulent respiratory infection. Culture revealed a *Staphylococcus aureus* coagulase positive. White blood cell

count was 15,200. Prior to surgery, the child was given 150,000 units of penicillin twice daily to control the respiratory infection. As a prophylactic measure, this was continued after the infection had subsided. Surgery was delayed by a heavy schedule and after two weeks there was a recurrence of his upper respiratory infection. Smear and culture of the exudate contained only *Ps. aeruginosa*, not sensitive to penicillin, streptomycin, or chloramphenicol, but very sensitive to polymyxin B (Aerosporin*). When this antibiotic was given in a dose of 2½ mg. per kilogram of body weight, the infection subsided in thirty-six hours.

### *Acute Lower Respiratory Tract Infection*

CASE 6.—A premature male infant of seven months gestation, weighing 3 pounds 4 ounces, was placed on prophylactic penicillin, 100,000 units daily, shortly after birth on Dec. 13, 1951. On Jan. 17, 1952, the child developed respiratory difficulty with marked sternal intercostal retraction. White blood cell count was 16,000. Eosinophil count was 778 per cubic millimeter. X-ray showed mottled densities throughout both lung fields. The predominant organism on nasopharyngeal culture was *Ps. aeruginosa* resistant to penicillin, streptomycin, aureomycin, terramycin, and chloramphenicol, and only slightly sensitive to polymyxin B. The latter antibiotic was nevertheless administered in a dose of 2.5 mg. per kilogram per day for a period of six days with no change in the clinical findings or radiological examination. The organism recovered was very sensitive to acetic acid and the patient responded to an environment of nebulized acetic acid.

CASE 7.—A 2½-year-old white female who had been in the nephrotic stage of glomerulonephritis for one year was admitted to Brooke Army Hospital on Feb. 28, 1949, because of a severe cough. Diffuse pneumonic infiltration was noted on x-ray examination. She had been receiving prophylactic penicillin, 100,000 units three times daily, for a period of months as an outpatient, because of recurrent respiratory infections. *Ps. aeruginosa* was the predominant organism in nasopharyngeal and sputum cultures. This organism was sensitive to streptomycin and the patient responded to 0.25 Gm. administered every six hours.

### *Chronic Lower Respiratory Tract Infection*

CASE 8.—A 9-year-old white male with bronchiectasis was admitted to the hospital on July 27, 1951, because of a recrudescence of symptoms, including fever, cough, and purulent sputum. The predominant organism at that time was a coagulase-positive *Staph. aureus*. With penicillin therapy, the patient improved and was discharged on oral penicillin, 100,000 units twice daily. He was readmitted on August 14 with another recrudescence. He was producing profuse amounts of greenish purulent material from which *Ps. aeruginosa* was recovered in pure culture. Fortunately this organism was sensitive to terramycin, and although the patient was critically ill for several weeks, his chest eventually became clear and his sputum nonpurulent. He has remained well on intermittent courses of terramycin since discharge from the hospital on Oct. 6, 1951.

## DISCUSSION

Additional cases could be cited, but these are typical of our recent experience with infection caused by *Ps. aeruginosa*. One factor these patients have in common is prolonged antibiotic therapy, usually penicillin.

Of all the potentially pathogenic bacteria, *Ps. aeruginosa* is one of the most resistant to chemotherapeutic and antibiotic agents. It has been shown

*Burroughs Wellcome & Co., Inc.

in experiences with intestinal antisepsis[5] and general antibiotic therapeusis[6, 7] that organisms resistant to an antibiotic increase enormously in number and become a predominant part of the local flora. When *Ps. aeruginosa* was the predominant organism isolated from the stools of patients with diarrhea, 81.9 per cent gave a history of having recently received antibiotic therapy.[8] Accompanying aureomycin therapy for cystic fibrosis of the pancreas, a decrease in frequency of staphylococcal infections and an increased frequency of death from Pseudomonas pneumonitis[9] have been observed. The appearance of infection symptoms due to gram-negative bacillary flora in the upper respiratory tract as the result of penicillin and broad spectrum antibiotic therapy of gram-positive respiratory infections has been reported by McCurdy and Neter.[10]

*Ps. aeruginosa* is resistant to many antibiotics and some strains show resistance to all antibiotics. Such infections give little hope for antibiotic help. A real risk of Pseudomonas infection must therefore be calculated in the prolonged use of penicillin or broad spectrum antibiotics.

Recognition of *Ps. aeruginosa* lesions clinically is necessary if a fatal outcome is to be avoided. Cutaneous lesions are sufficiently characteristic to be recognizable on sight. The primary lesion appears innocuous and resembles a small, ecchymotic area which rapidly becomes necrotic and ulcerated. The ulcer then spreads around the periphery with a minimum amount of reaction in the adjacent tissues (Fig. 1, *A*). Although the patient may be afebrile, blood cultures at this point are usually positive. If the process is not then checked, the patient develops pyemia and multiple metastatic lesions (Fig. 1, *B*). The ulcers in the gastrointestinal tract in Case 4 resembled exactly those seen on the skin. Destruction of the deeper layers of the bowel, by the burrowing action of these ulcers, resulted in the escape of gas between muscle layers (pneumatosis cystoides intestinalis). The latter is also an unusual condition, less than twenty-five cases having been reported in children.[11]

A biopsy specimen was taken from the edge of a black necrotic lesion on the buttocks of Case 2 from which cultures showed Pseudomonas, Staphylococci, and gamma Streptococci. Sections from this biopsy stained by tissue-gram technique showed skin and underlying areolar tissue (Fig. 2). The epidermal cells were separated as by edema. There was separation of the collagen fibers. Throughout the dermis and subcutaneous tissue many scattered, long, gram-negative rods were seen. These rods, massed in dense clusters about the vascular lumens, were interpreted to be Pseudomonas. Gram-positive cocci were not seen in this specimen. There was no leukocyte response.

This histological picture is similar to that described by Fraenkel[1] in a study of twenty-six cases of Pseudomonas infections of which sixteen showed ecthyma gangrenosum. He concluded that the finding of rod-shaped bacteria in the walls of the blood vessels at the site of infection established the anatomical diagnosis of *B. pyocyaneus* infection without cultural identification. The clinical picture in any site was that of circumscribed necrosis.

The choice of therapy is dependent upon careful in vitro sensitivity studies. In spite of its toxicity, Aerosporin[12] is indicated in severe infections in view of the poor prognosis, provided the organism is sensitive to this antibiotic. Work previously published by two of us[13] suggests that combined therapy with penicillin, streptomycin, and sulfadiazine may be effective even though the organism is moderately resistant to all three. In vitro, *Ps. aeruginosa* is inhibited, to a large extent, in the presence of a combination of the three drugs even though it grows well in the presence of any one or other combination of them. It has been shown that drug resistance to very high concentrations develop rapidly from one to three culture transfers when only one of the drugs was employed. When the three drugs were combined, this resistance did not develop until from six to nine transfers had been made. In Case 3, when attempts were made to discontinue any of the three, blood cultures again became positive and multiple abscesses appeared.

Prolonged treatment is usually necessary. When effective therapy is employed, the blood culture becomes negative, and metastatic abscesses are absorbed. The ulcerations of the skin become clean and necrosis ceases. The granulation tissue which remains becomes more normal in appearance and the ulcers heal. Residual tissue loss and marked scarring, may, however, be evident. Such patients show agglutination titers as high as 1:1,000 against the responsible organism.[14]

## CONCLUSIONS

1. Pathogenicity of *Ps. aeruginosa* seems to be enhanced by prolonged and indiscriminate antibiotic therapy.

2. The clinical and microscopic appearance of the skin lesions produced by this organism are very characteristic.

3. Successful therapy is dependent upon careful in vitro sensitivity studies.

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# CONGENITAL PULMONARY STENOSIS WITHOUT CYANOSIS

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PULMONARY stenosis is most often associated with other cardiac defects, such as dextroposition of the aorta, ventricular septal defect, or atrial septal defect.[1] Patients having, in addition to pulmonary stenosis, one or more of these associated defects are usually cyanotic from birth or early childhood. Stenosis of the pulmonary valve may occur as an isolated lesion or associated with patency of the foramen ovale; these patients may be acyanotic throughout life or be cyanotic only terminally. It is this latter group of patients who will be discussed in this review.

Valvular pulmonary stenosis as an isolated lesion or associated with an interatrial communication has been considered rare.[1, 2] In Maud Abbott's[1] series of 1,000 patients with congenital heart disease, 110 patients had pulmonary stenosis and eighty-five of these were associated with an interventricular septal defect. Of the other twenty-five patients, sixteen were associated with an interatrial septal defect and nine patients had isolated pulmonary stenosis with intact septa. In 1949 Greene and associates[3] reviewed the literature and were able to find only sixty-eight cases of proved isolated pulmonary stenosis. Likewise, in over 50,000 autopsies performed at the Department of Pathology at the University of Minnesota, only three cases of isolated pulmonary stenosis have been found. Dow and co-workers[4] had previously commented upon the disparity which exists between the infrequent pathological diagnosis and the apparent frequency of the clinical cases.

With the development of newer techniques in cardiac surgery, it is apparent that more specific diagnoses must be made in that group of patients commonly referred to as having "acyanotic congenital heart disease." Almost without exception, the patients in this review were initially diagnosed as having a "septal defect." Adams and associates[5] have recently pointed out the value of newer diagnostic aids in patients with pulmonary stenosis. It is the purpose of this review to reemphasize the importance of recognizing this lesion and to discuss the clinical and laboratory features as well as the prognosis, course, and therapy of patients with isolated pulmonary stenosis.

## MATERIAL AND METHODS

From the material of this clinic, twenty-three patients with pulmonary stenosis in whom cyanosis was not present will be reviewed. The diagnosis was confirmed by cardiac catheterization in seventeen patients, by surgery without catheterization in three patients, and the clinical and laboratory findings in the remaining three patients are quite typical of the lesion.

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This work was performed under a cooperative agreement between the University of Minnesota and the National Heart Institute.

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TABLE I. CLINICAL DATA ON TWENTY-THREE PATIENTS WITH PULMONARY STENOSIS WITHOUT CYANOSIS

| | | | ELECTROCARDIOGRAM | | | ROENTGENOGRAMS | | | | | CATHETERIZATION | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PATIENT | AGE (YR.) | DYSPNEA | RIGHT AXIS | R. V. H. | PEAKED $P_2$ | R. V. H. | P. A. SIZE | L. P. A. >R. P. A. | LUNG MARKS | DIAGNOSIS | R. V. PRESS | P. A. PRESS | F. H. SAT. (%) | SURGERY |
| J. N. | 18 | 3+ | + | + | + | 4+ | 2+ | 0 | N | Sugg. | 160/20 | 12/8 | 98 | + |
| T. R. | 8 | 1+ | + | + | 0 | 2+ | 1+ | 0 | N | Sugg. | 80/0 | 7/3 | 96 | + |
| J. A. | 15 | 2+ | + | + | + | 3+ | 3+ | + | N | Typ. | 145/0 | 6/5 | 95 | + |
| K. G. | 14 | 1+ | + | + | 0 | 3+ | 3+ | + | N | Typ. | 117/-11 | 11/4 | -- | + |
| S. K. | 11 | 3+ | N | + | + | 3+ | 3+ | + | N | Typ. | 260/0 | 12/10 | 100 | + |
| R. S. | 18 | 2+ | + | ± | 0 | 3+ | 3+ | + | N | Typ. | 150/0 | 24/10 | 100 | + |
| I. O. | 23 | 0 | + | N | 0 | 2+ | 2+ | + | N | Typ. | 90/0 | 25/15 | 94 | + |
| W. M. | 17 | 2+ | + | + | + | 3+ | 3+ | + | N | Typ. | 196/16 | 17/5 | -- | + |
| D. B. | 5 | 0 | + | + | 0 | 2+ | 3+ | + | N | Typ. | -- | -- | -- | + |
| S. L. | 5 | 1+ | + | + | 0 | 2+ | 2+ | + | N | Typ. | -- | -- | -- | + |
| R. E. | 29 | 1+ | + | + | + | 3+ | 3+ | + | N | Typ. | -- | -- | -- | + |
| D. M. | 14 | 1+ | + | + | 0 | 3+ | 3+ | + | N | Typ. | 90/25 | 16/14 | 95 | 0 |
| L. R. | 12 | 0 | + | + | 0 | 2+ | 2+ | 0 | 1+ | Sugg. | 25/10 | 3/2 | 100 | 0 |
| J. R. | 7 | 1+ | N | ± | 0 | 1+ | N | 0 | N | Atyp. | 50/0 | 20/6 | 94 | 0 |
| A. C. | 17 | 0 | + | + | 0 | 2+ | 2+ | + | N | Typ. | 60/8 | 6/5 | 100 | 0 |
| R. J. | 5 | 0 | N | ± | 0 | 1+ | 1+ | 0 | 1+ | Sugg. | 45/-10 | 12/8 | 100 | 0 |
| C. J. | 20 | 2+ | + | + | 0 | 2+ | 4+ | + | N | Typ. | 91/7 | 15/- | 95 | 0 |
| H. K. | 9 | 0 | + | + | 0 | 2+ | 2+ | + | N | Typ. | 75/0 | 8/5 | 95 | 0 |
| W. Mc. | 6 | 0 | + | + | 0 | 2+ | 3+ | + | N | Typ. | 34/-4 | 10/4 | -- | 0 |
| A. H. | 17 | 2+ | -- | -- | -- | 2+ | 2+ | 0 | N | Sugg. | 40/-8 | 12/2 | 99 | 0 |
| K. R. | 6 | 0 | + | + | 0 | 2+ | 1+ | + | N | Typ. | -- | -- | -- | 0 |
| B. M. | 3½ | 0 | + | + | 0 | 1+ | 3+ | + | N | Typ. | -- | -- | -- | 0 |
| R. D. | 2 | 0 | + | + | 0 | 1+ | 3+ | + | 1+ | Sugg. | -- | -- | -- | 0 |

+ = Present or positive.
0 = Absent or negative.
- = Data not obtained.
± = Interpretation open to question.
N = Normal.

R. V. H. = Right ventricular hypertrophy.
P. A. = Pulmonary artery.
F. A. = Femoral artery.

The patients were evaluated by the clinical history, the physical examination, the electrocardiogram, the roentgenological examination, by cardiac catheterization, and by oximeter studies as described in previous reviews.[3-8]

Eleven patients have had surgery, and a six-month follow-up of five patients will be briefly discussed.

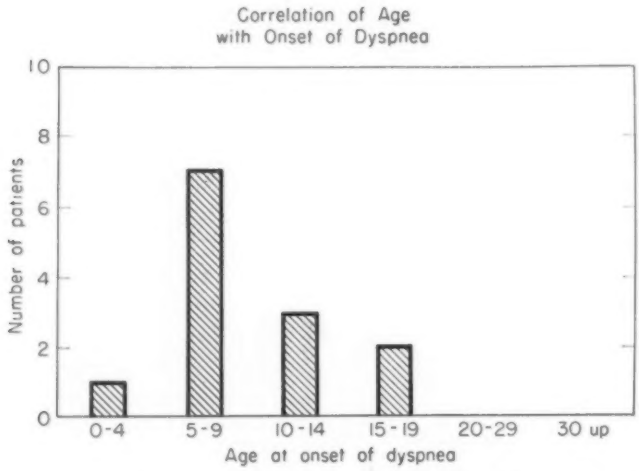


Fig. 1.—Graph showing the age of onset of dyspnea. Note the number of patients who developed dyspnea before 10 years of age.

## RESULTS

*Clinical Findings.*—A summary of the clinical findings in the twenty-three patients can be seen in Table I. There appears to be no sex predisposition. Twelve patients were males and eleven were females.

The age range was from 20 months to 29 years. Fifteen of the twenty-three patients were under 15 years of age, only two patients were over 20 years of age, and no patients were over 30 years of age.

The onset of symptoms was rather insidious and no patients developed symptoms until early childhood. Thirteen of the patients ultimately developed symptoms and ten patients were free of symptoms at the time of follow-up. Dyspnea on exertion was the typical complaint and was more uniformly present in the older age group. Only three of nine patients over 15 years of age were symptomatic. The dyspnea varied from mild (1+) with only minimal limitation of activity to marked (4+) with almost complete incapacitation. Fig. 1 shows graphically the relationship of the age of the patient to the onset of dyspnea.

Three patients experienced precordial pain on exertion and another patient (29 years of age) had only mild dyspnea but had recurrent palpitation and dizziness and subsequently developed several episodes of paroxysmal ventricular tachycardia associated with heart failure.

No patients gave a history of squatting as is quite typical of patients with tetralogy of Fallot.

Analysis of the growth and development by the Wetzel Grid technique in eighteen of the patients can be seen in Table II. According to this method, the data from the majority of patients fell into the $A_1$, M, $B_1$ channels or the average physique channels and the speed of growth appeared to be normal.

None of the twenty-three patients was cyanotic, either by clinical appearance or by evidence of desaturation of arterial blood. Two additional patients were acyanotic clinically, but had slight desaturation of their arterial blood, suggesting the probability of minimal patency of the foramen ovale.

Table II. Analysis of the Physique and the Speed of Growth

| Lowest channel | $A_4$ | $A_3A_2$ | $A_1$M $B_1$ | $B_2$ | $B_3$ | $B_4$ | Total No. of Patients |
|---|---|---|---|---|---|---|---|
| No. of patients | 0 | 1 | 15 | 1 | 1 | | 18 |
| Lowest auxodrome | 0-2% | 2% | 15% | 67% | 82% | 98% | |
| No. of patients | | 1 | 4 | 9 | 2 | 2 | 18 |

Clubbing of the digits was uniformly absent. Only three of the patients had a precordial bulge of the chest. A systolic thrill was palpable in the pulmonary region in fifteen patients or approximately two-thirds of the cases.

A loud (grade 3-4) systolic murmur in the pulmonic region was present in all patients. The pulmonary second sound was decreased in intensity or obscured by the murmur in all but one patient. Diastolic murmurs were uniformly absent.

The blood pressure was not considered to be significantly abnormal in any of the patients. Only two of the patients had extracardiac anomalies. One patient was a deaf-mute and the other patient had neurofibromatosis.

The clinical history and findings of the patients in this series were quite similar to comparable patients as reported in previous reviews.[3, 4, 9-12]

*Electrocardiographic Findings.*—Electrocardiograms were available for review on twenty-two of the twenty-three patients. Two patients had only the standard lead tracings, the other twenty patients had additional unipolar lead tracings.

Axis deviation greater than 90 degrees was present in nineteen of the twenty-two tracings. Quite definite evidence of right ventricular hypertrophy as determined by the standards of Sokolow and Lyon[6] and Veasy and Adams[7] was present in eighteen of the twenty patients with unipolar lead tracings. The tracing of one patient was suggestive of right ventricular hypertrophy and one patient's tracing showed no evident hypertrophy. Abnormal elevation of the P wave in Lead II was present in five tracings. Peaking of the P wave without abnormal elevation was present in the majority of patients. Right bundle branch block was present on the tracings of two patients.

These results with regard to the electrocardiographic findings are comparable to those mentioned in previous reviews.[5, 9, 12] Orme and Adams[14] have recently attempted to correlate the electrocardiographic findings with intracardiac pressures in patients with congenital heart disease. In patients with isolated pulmonary stenosis, they found only slight correlation of electrocardiographic right ventricular

hypertrophy with right ventricular pressure as determined by cardiac catheterization.

*Roentgenological Findings.*—The lesion of isolated pulmonic stenosis appears to be also a roentgenologic entity and when the characteristic findings are present, add considerably to confirming the clinical diagnosis. The typical roentgen findings are: right ventricular hypertrophy, a disproportionate enlargement of the main pulmonary artery segment and the left root shadow as compared to the right root shadow, and normal or slightly decreased diameter of the peripheral vascular markings (see Figs. 2 and 3). These characteristic findings were present in sixteen of the patients, in six cases the roentgen findings were suggestive, and in one case the findings were atypical.

The right ventricle was enlarged by x-ray in all of the patients. The main pulmonary artery was abnormally prominent in twenty-two of the twenty-three patients. A disproportionate enlargement of the left root shadow as compared to the right root shadow was present in seventeen of the patients' x-rays. Twenty patients were considered to have normal peripheral vascular markings, and three patients had decreased peripheral vascular markings by x-ray.

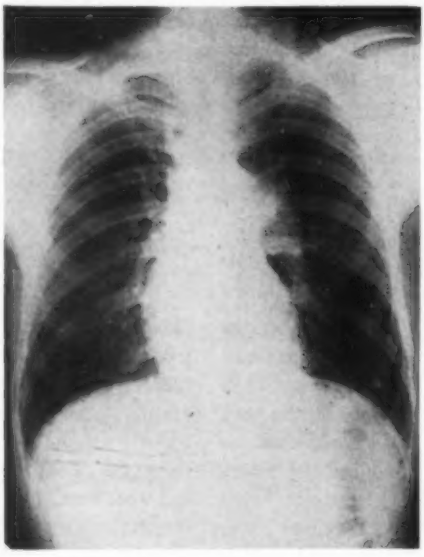

Fig. 2.—Roentgenogram of patient C. J., a 20-year-old male, showing the typical changes found in valvular pulmonary stenosis; right ventricular hypertrophy; enlargement of the pulmonary artery segment; a disproportionate enlargement of the left pulmonary artery over the right; and normal peripheral vascular lung markings.

Angiocardiography was performed on only two patients as it was felt that this procedure was usually not necessary to confirm the diagnosis. Other investigators[4, 9, 11, 15] have commented previously on the rather typical roentgen findings.

*Physiological Findings.*—Physiological studies are necessary to con-

firm the diagnosis of isolated pulmonary stenosis based on clinical evidence. Of physiological aids, cardiac catheterization, arterial oxygen saturation, cardiac output, oximeter studies, and circulation times are the most useful. The methods of performing these procedures have been previously described.[3, 4, 5, 8, 9, 16]

Cardiac catheterization was performed on seventeen patients. None of these patients had evidence of an additional lesion complicating the pulmonary stenosis. In the fourteen pa-

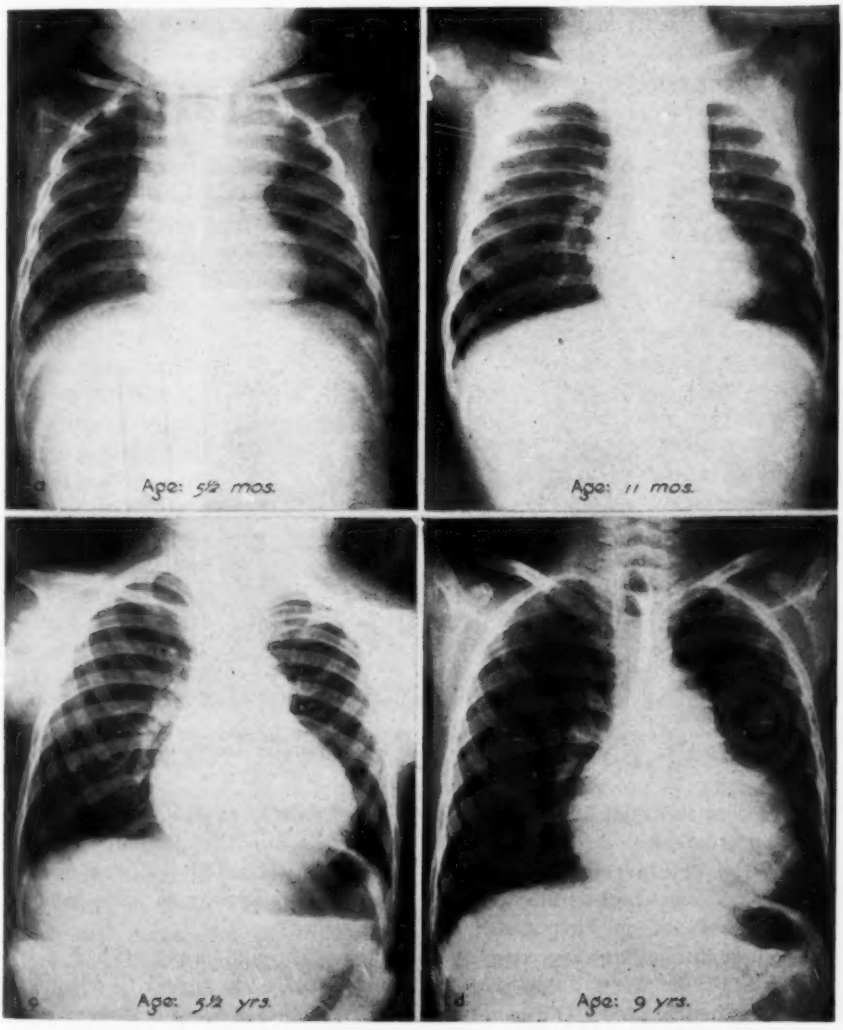


Fig. 3.—Roentgenograms of patient S. K., at 5½ months, 11 months, 5½ years, and 9 years, showing progressive cardiac enlargement with age. Note that in early infancy the so-called "poststenotic dilatation" of the main pulmonary is not as evident as it is later.

tients where an arterial blood sample was obtained, the arterial oxygen saturation was within normal limits (above 94 per cent).[17] The point of stenosis was considered to be valvular, not infundibular, in all of the patients who were catheterized. The right ventricular pressure was elevated in sixteen of the patients and varied from 40/–8 to 260/0 mm. of mercury. In the one remaining catheterized patient, the right ventricular pressure was 25/10 mm. of mercury and the pulmonary artery pressure was 3/2 mm. of mercury. The pressure findings in this patient are somewhat similar to those patients reported to have idiopathic dilation of the pulmonary artery although the pulmonary artery pressure in this patient is lower than in the reported cases.[3] In addition, he was symptomatic, he had enlargement of the right ventricle on x-ray, and he had suggestive right ventricular hypertrophy on the electrocardiogram.

In four patients tested, oximeter studies were within normal limits.

*Therapy.*—Eleven patients have had surgery in an attempt to relieve the stenosis of the pulmonary valve. Two patients had a dissection type pulmonary valvulotomy[18] and nine patients had a Brock[19, 20] type of valvulotomy.

Fig. 4.—Roentgenogram of patient S. K., 10 years, 10 months of age, one year following a pulmonary valvulotomy. Note decrease in cardiac size and increase in lung markings in comparison with Fig. 3, *d*.

One patient expired at the time of surgery while the pulmonary artery was being exposed. The remaining ten patients appear to have benefited from surgery.

Five patients have not had a sufficient follow-up period to adequately evaluate the effects of surgery. The remaining five patients have been followed from six to twenty months since

the time of their surgery. These five patients have had striking symptomatic improvement. Three of them had moderate to marked dyspnea while two had mild dyspnea before surgery. Following surgery, the five patients stated that their dyspnea was much improved and all of them are taking part in gym and athletic activities with only minimal to mild symptoms. Two patients had precordial pain with exertion preoperatively and have experienced no pain postoperatively.

The systolic thrill and murmur have remained unchanged since surgery. Four of the five patients have developed soft blowing diastolic murmurs along the left upper sternal border probably due to some pulmonary valve insufficiency. It is believed that sufficient time has not elapsed since surgery to significantly alter the preoperative roentgen and electrocardiographic findings.

Two patients have had postoperative determination of their right ventricular pressure. In one patient the right ventricular pressure was reduced from 260/0 preoperatively to 60/0 two weeks after surgery (see Fig. 4). In the other patient, the preoperative right ventricular pressure was 99/11 mm. of mercury, and three months after surgery, it had decreased to 58/6 mm. of mercury.

## DISCUSSION AND CONCLUSIONS

As evidenced by recent clinical reports,[5, 9, 12] isolated pulmonary stenosis appears to be a relatively common congenital cardiac defect. These patients are typically acyanotic although occasional patients may have cyanosis late in their course due to "peripheral" cyanosis due to stasis of blood with slowing of the circulation.[11] Patients with minimal patency of the foramen ovale associated with pulmonary stenosis may have slight desaturation of arterial blood without visible clinical cyanosis.

Allanby and Campbell[11] and Blackett and associates[9] have described clearly the course of patients with pulmonary stenosis with intact ventricular septums. The patients are almost uniformly born without other physical defects and are apparently normal at birth. The heart murmur is usually discovered some time after birth upon a routine physical examination. They usually develop normally and may have no symptoms until late childhood or early adulthood although almost one-half of them complain of dyspnea on exertion by the time they reach 15 years of age. Some may just tire more easily than their playmates. The degree of the stenosis determines the disability and prognosis. The majority of the patients die of their cardiac disease. In Greene's[3] series, at least twenty-six of sixty-eight patients died of heart failure; eight of his patients died of subacute bacterial endocarditis. Leech[13] and Blackford and Parker[21] mention pulmonary stenosis as a cause of sudden death. The average age at death in Abbott's[1] series was 22 years of age for those with isolated pulmonary stenosis and 18 years of age for those with an associated atrial septal defect. In Greene's[3] series of sixty-three cases of isolated pulmonary stenosis where the age at the time of death was known, the average life span was 26 years. Only seven patients lived past 50 years of age; one patient lived until 75 years of age.

The diagnosis may be highly suggested by the history of dyspnea on exertion, the presence of a thrill and systolic murmur in the pulmonary region and with obliteration of the pulmonary second sound by the murmur. The diagnosis is often quite adequately confirmed by the presence of right axis deviation and right ventricular hypertrophy on the electrocardiogram and the presence of right ventricular hypertrophy, a prominent main pulmonary artery segment, and a disproportionate enlargement of the left root shadow as compared with the right root shadow on roentgen examination. Additional physiological studies, such as cardiac catheterization, oximeter studies, arterial oxygen saturation, and circulation tests, prove the diagnosis and rule out complicating lesions.

As evidenced by the markedly decreased life expectancy, nonsurgical therapy is not adequate for the majority of patients. A suitable surgical method of relieving these patients has been proposed by Brock.[19, 20] The authors agree with Blackett and coworkers[9] that those patients with marked symptoms, evidence of cardiac hypertrophy on roentgen and electrocardiographic studies, and increased right ventricular pressure should have the benefit of surgery. In our experience, this group has obtained remarkable short-term benefit from surgery. In the light of present knowledge, those patients with mild to moderate symptoms, with mild to moderate roentgen and electrocardiographic changes, and right ventricular pressure increase, must be totally evaluated, but probably should have surgery. Those with minimal symptoms and little or no change on other tests can probably be safely observed until the long time follow-up on those patients who have had surgery has been evaluated.

Since surgery at the present time has been aimed mainly at the valvular type, it is exceedingly important to differentiate between the various types of stenosis. Keith[22] first described the various types of pulmonary stenosis and described three varieties. According to him the stenosis may be at the valve, high in the infundibulum, or low in the infundibulum creating an infundibular chamber between the right ventricle and the pulmonary valve. Valvular stenosis is usually seen pathologically as a concave, buttonlike, diaphragm deformity with a central opening protruding into the root of the main pulmonary artery. Occasionally the valves are merely thickened and irregular with a slitlike opening.

Allanby and Campbell[11] and Burke and collaborators[23] have pointed out that patients with tetralogy of Fallot usually have infundibular stenosis. Allanby and Campbell[11] state that the stenosis is usually valvular when the interventricular septum is intact. Others[3, 4, 22] have pointed out that often the valvular and infundibular types are associated. It has been the authors' experience, even when infundibular stenosis is presumably associated with valvular stenosis, that surgery aimed at relieving the obstruction at the valve region has helped to relieve these patients of their symptoms.

## SUMMARY

1. Twenty-three acyanotic patients with isolated pulmonary stenosis have been presented.

2. The diagnosis was confirmed by cardiac catheterization in seventeen patients, by surgery in three patients, and by clinical, roentgen, and electrocardiographic findings in three patients.

3. The clinical histories, physical findings, roentgen studies, electrocardiographic results, and physiological studies have been presented.

4. The frequency, course, prognosis, cause of death, and type of stenosis have been reviewed.

5. The results have been presented of a six-month follow-up on five of the patients who had a valvulotomy.

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# GROWTH STUDY OF CHILDREN WITH THE TETRALOGY OF FALLOT

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REFERENCE is frequently made to the small stature and poor physique of children with congenital heart disease. Until recently, however, no data have been collected which objectively measure their growth. The advent of surgery undoubtedly stimulated the interest in growth with the hope that it would be favorably influenced. Patent ductus arteriosus has been investigated more thoroughly than other cardiovascular anomalies.[1, 2, 3, 4, 5] Cyanotic congenital heart disease, contrarily, has not received as much attention. In a report on an analysis of 200 cases of mixed types of cyanotic congenital heart disease Campbell and Reynolds[6] stated that these patients were both shorter and of less weight than the average for their age. Averages were used that did not allow for normal variation and individual evaluation of growth was not attempted. Baker and associates[7] reported an analysis of fifty cases of cyanotic congenital heart disease studied pre- and postoperatively as regarded growth. Again study of individual growth patterns was not made and allowance for normal variations was not considered. Time is an important factor in studying growth as the ultimate attainment is the object of interest rather than the minor variations in growth that may occur over short periods of time. Consequently any helpful study of postoperative growth in the cyanotic congenital heart group has awaited the passage of time since surgery has been available only relatively recently.

In searching for a means of evaluating the data collected on the patients under study, the Wetzel Grid was found to afford the most complete analysis. It offered an analysis of both body physique type and speed of growth with the use of only periodic measurements of height and weight. Deviations from the individual's own pattern could be easily detected and expressed in numerical terms.

The material used included twenty controls and forty-seven patients who were studied both pre- and postoperatively. Patients chosen for study included all those seen in the University of Minnesota Hospitals up to Jan. 1, 1951, with a diagnosis of the tetralogy of Fallot, upon whom sufficient data had been collected. Adequate study included enough height and weight values to cover ten developmental levels on the physique grid. A deviation of one physique channel in ten developmental levels was considered significant. A deviation of three developmental levels from the patient's own auxodrome was considered to be a significant deviation in speed of growth. These are according to Wetzel's standards.[8] The twenty controls, all of whom had the tetralogy of Fallot, included five patients who were not operated upon, usually because of a

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This work was performed under a cooperative agreement between the University of Minnesota and the National Heart Institute, U. S. Public Health Service, Bethesda, Md.

declination on the part of the parents, and fifteen patients who were later operated upon but were followed for a sufficient period of time preoperatively to serve as their own controls. There was a total of sixty-six patients operated upon. Not all of these patients had subsequent growth records. Forty-seven had sufficient data to evaluate the effect of surgery upon growth. The others may be included in any evaluation of the general growth status of children with cyanotic congenital heart disease.

TABLE I. PHYSIQUE AT TIME OF SURGERY OR MOST CURRENT LEVEL REACHED WITHOUT SURGERY

| PHYSIQUE CHANNEL | DESCRIPTION | NO. OF PATIENTS |
|---|---|---|
| $B_4$ | Poor | 4 |
| $B_3$ | Borderline | 9 |
| $B_2$ | Fair | 19 |
| $B_1$ | Good | 12 |
| M | Good | 10 |
| $A_1$ | Good | 4 |
| $A_2$ | Stocky | 1 |
| $A_3$ | Stocky | 3 |
| $A_4$ | Obese | 4 |

It can be seen from Table I that many of the sixty-six patients operated upon had fair physiques at the time of surgery. There were only twenty-six that had good physiques. This confirms our impression that the majority of children with this difficulty do not have good physiques. That the majority are not very poor but fall in the fair category with over one-third of them in the good category is probably the most significant deduction from these data. The fact that these patients were severely enough restricted in exercise tolerance and of such poor general health to be brought to the hospital for plastic cardiovascular surgery categorizes them as a severely debilitated group. It seems paradoxical that their physiques are so good. A study of the speed of growth attained by these same patients at the time of surgery shows the average auxodrome to be 73 per cent which means that 72 per cent of children are growing at a faster rate. The mean value is 80 per cent and the distribution may be seen in Table II. It is clear that more children with this anomaly grow slowly than is true of the general population.

TABLE II. AUXODROME ATTAINMENT AT TIME OF SURGERY OR MOST CURRENT LEVEL REACHED WITHOUT SURGERY

| AUXODROME LEVEL (PER CENT) | NO. OF PATIENTS |
|---|---|
| 2 | 1 |
| 3-15 | 3 |
| 16-67 | 12 |
| 68-82 | 25 |
| 83-98 | 13 |
| 99-100 | 12 |

Studying the slope of the speed of growth curves of the controls shows us that the majority had a loss greater than three developmental levels from their expected auxodrome using the initial value as the expected auxodrome. The mean age for these children when the last values were obtained was 6 years 4 months with an average of 5 years 7 months, and a range of from 5 months to 12 years 3 months. There were only three children who showed a gain in speed of growth. These children were younger. There were four children who maintained their original speed of growth. Their ages were older than both the group that lost and the group that gained speed. There were no very young children that showed a gain in speed of growth. There were three children over 9 years of age that showed no loss or gain. For the most part this information seems to indicate that children with the tetralogy of Fallot, when studied individually in reference to their previous speed of

growth, show a steadily declining rate of growth as well as a generally slower speed as a group.

That a larger variance in height and weight must occur to cause a change in physique is borne out by studying the physiques of the same twenty controls. Only four of them lost physique, eight gained, and eight maintained their same physique over the period of time studied.

The data collected upon those forty-seven patients operated upon and upon whom sufficient height and weight values had been collected are summarized in Table V. The surgical procedures done upon these patients included the Blalock-Taussig type procedure upon forty-four, the Brock procedure upon two, and only thoractomy upon one patient because of inability to complete the intended procedure

TABLE III. SPEED OF GROWTH OF CONTROLS

| | GAIN IN SPEED | LOSS IN SPEED | NO CHANGE IN SPEED |
|---|---|---|---|
| No. of patients | 3 | 13 | 4 |
| Mean age | 4 yr. 5 mo. | 6 yr. 4 mo. | 9 yr. 6 mo. |
| Average age | 4 yr. 5 mo. | 5 yr. 7 mo. | 9 yr. |
| Age range | 3 yr 11 mo. to 4 yr. 11 mo. | 5 mo. to 12 yr. 3 mo. | 4 yr. 10 mo. to 12 yr. 3 mo. |

TABLE IV. PHYSIQUE PROGRESS OF CONTROLS

| | GAIN IN PHYSIQUE | LOSS IN PHYSIQUE | NO CHANGE IN PHYSIQUE |
|---|---|---|---|
| No. of patients | 8 | 4 | 8 |
| Mean age | 4 yr. 10½ mo. | 11 yr. 10 mo. | 5 yr. 5 mo. |
| Average age | 4 yr. 5 mo. | 9 yr. 11 mo. | 5 yr. 3 mo. |
| Age range | 5 mo. to 7 yr. 11 mo. | 3 yr. 11 mo. to 12 yr. 3 mo. | 1 yr. 9 mo. to 8 yr. 1 mo. |

TABLE V. SPEED OF GROWTH OF PATIENTS OPERATED UPON

| | GAIN IN SPEED | LOSS IN SPEED | NO CHANGE IN SPEED |
|---|---|---|---|
| No. of patients | 14 | 21 | 12 |
| Mean age | 8 yr. 4 mo. | 7 yr. 4½ mo. | 6 yr. 6 mo. |
| Average age | 8 yr. 7 mo. | 7 yr. 10 mo. | 6 yr. 4 mo. |
| Age range | 3 yr. 11 mo. to 13 yr. 8 mo. | 3 yr. 1 mo. to 13 yr. 4 mo. | 6½ mo. to 13 yr. 4 mo. |
| No. of operative successes | 12 | 19 | 11 |
| No. of operative failures | 2 | 2 | 1 |

In general, those who gained or remained in the same physique channel were younger.

The lack of correlation between the per cent that lost in speed of growth and the per cent that lost physique is unclear but according to Wetzel[9] the speed of growth is a more sensitive indication of growth deficit or gain than is physique type.

due to technical difficulties. All patients had height and weight values collected postoperatively which gave grid values at least ten developmental levels beyond the grid values attained at the time of surgery; thus sufficient time had elapsed to eclipse the influence of the surgical procedure per se as well as the hospitalization and psychic factors attendant therein. Ref-

erence to Table V shows that almost one-half of these patients operated upon had a loss in speed of growth after surgery. The mean age at the time of surgery was 7 years 4½ months with an average age of 7 years 10 months, and a range of from 3 years 1 month to 13 years 4 months. Nineteen of the twenty-one patients in this group were considered operative successes as judged by notable increase in exercise tolerance. Slightly more than one-half of these operated upon showed a gain or no change in speed of growth. There were three operative failures in these groups as compared with two in the group that lost speed. It appears as if surgery does not influence the speed of growth nor is the time at which the operation is done an important factor influencing subsequent growth.

Table VI. Physique Progress of Patients Operated Upon

| | GAIN IN PHYSIQUE | LOSS IN PHYSIQUE | NO CHANGE IN PHYSIQUE |
|---|---|---|---|
| No. of patients | 12 | 20 | 15 |
| Mean age | 9 yr. 3 mo. | 6 yr. 6 mo. | 7 yr. 1 mo. |
| Average age | 8 yr. 9 mo. | 6 yr. 2 mo. | 9 yr. 11 mo. |
| Age range | 3 yr. 5 mo. to 13 yr. 8 mo. | 6½ mo. to 8 yr. 10 mo. | 3 yr. 1 mo. to 13 yr. 4 mo. |
| No. of operative successes | 12 | 17 | 13 |
| No. of operative failures | 0 | 3 | 2 |

Likewise, among these patients operated upon there were almost equal numbers of patients with loss in physique as compared with these who showed a gain in physique or no change following surgery. Similarly, age at the time of surgery did not seem to be an important factor influencing the course of physique. Also it should be noted that surgery was successful in a large majority of these patients as judged by considerable increase in exercise tolerance.

The fact that many children with this disorder continue to lose in speed of growth following plastic cardiovascular surgery which renders them remarkably improved in most cases in their general feeling of well-being, appetite, exercise ability, and vigor makes one wonder whether these children are influenced in their growth not alone by anoxia secondary to their cardiac anomaly but in addition or solely by a more subtle constitutional deterrent.

It was thought that it would be of value to know if there was a correlation between exercise ability and changes in physique pattern and speed of growth among the controls. Exercise ability was graded 1+ to 6+ with 1+ meaning inability to be out of bed and requiring oxygen much of the time. Six plus meant normal full activity. Two plus equalled capacity to be out of bed and walk a few steps. Three-plus ability allowed the patient to walk six to twelve blocks but it was difficult for him to climb stairs and he had to squat frequently while playing. Four-plus activity meant slightly greater extent but patient was unable to run more than very short distances. Five-plus activity equalled ability to take part in full activity including competitive sports but demanded more than usual rest periods. Examination of Table VII shows that although

eight of the thirteen patients who showed a loss in speed of growth had 3+ or less exercise capacity, five of them had 4+ and 5+ capacity. Of the three that gained in speed of growth two had 2+ capacity and one had 4+ capacity. Similarly among the controls there is no correlation between physique gain or loss over the period of time studied and their exercise ability.

Racial characterization of the sixty-six cyanotic patients operated upon was not done. However, the population from which these patients came is sufficiently heterogeneous and the numbers are sufficiently large to prevent weighting of the statistics by one particular body build such as the short stocky or the tall thin types. However, such selection would not affect the individual studies of growth which re-

TABLE VII. ACTIVITY ABILITY OF PATIENTS OPERATED UPON

| ACTIVITY ABILITY | NO. PATIENTS WITH GAIN IN GROWTH SPEED | NO. PATIENTS WITH LOSS IN GROWTH SPEED | NO. PATIENTS WITH NO CHANGE IN GROWTH SPEED | NO. PATIENTS WITH GAIN IN PHYSIQUE | NO. PATIENTS WITH LOSS IN PHYSIQUE | NO. PATIENTS WITH NO CHANGE IN PHYSIQUE |
|---|---|---|---|---|---|---|
| 0 | | 1 | | | | 1 |
| 1-2+ | 2 | 6 | 2 | 5 | 2 | 3 |
| 2-3+ | | 1 | 1 | 2 | | |
| 3-4+ | 1 | 3 | | 1 | 1 | 1 |
| 4-5+ | | 2 | 1 | | 1 | 3 |
| 6+ | | | | | | |

## DISCUSSION

Since it has been observed that a large number of children with the tetralogy of Fallot who live through infancy do equally well or progressively better during the subsequent few years it was wondered whether knowledge of their growth during this period unoperated upon and also operated upon would be important influencing factors in deciding the time at which surgery should be done. The results of this study do not indicate that surgery has any effect upon growth. The fact that almost one-half of the patients operated upon showed a gain or remained the same in growth speed and physiques does not have the significance as does the fact that the other one-half upon whom surgery was equally successful showed continued loss in growth speed and physique.

late the patient's progress not in terms of the rest of the population but only with his own previous pattern.

Another factor influencing growth is infection. Wetzel[9] has beautifully demonstrated the effect of infection on both physique and speed of growth, the latter being the most sensitive indication of disease. That patients with cyanotic heart disease have much difficulty with respiratory disease must be recognized by all that care for them. The majority of those patients in this study who were operated upon and followed postoperatively had fewer respiratory infections and handled those that they did have much better than preoperatively. Thus it would seem that this would be another factor aiding the growth of those operated upon and add to the confusion in attempting to answer the question, "Why don't these children grow better postoperatively?"

Comparing an individual's gain or loss in growth with his own previous pattern of growth gives us much more information than individual measurements compared with the population at large. Study of the effect of any procedure or environmental influence upon growth by comparing weight and height values with standards for a normal group of children is not valid as there are wide normal variations from the so-called normal. The most important consideration is the constancy of the individual's own pattern. The fact that a majority of patients studied in this investigation did not show an increase in rate of growth or improvement in physique after surgery but rather a continued decline in growth speed and physique value is significant whether the cause for the continued decline be due to persistent abnormal hemodynamics attendant with the Blalock-Taussig operation or due to extracardiovascular causes. More light will perhaps be shed on this question when a sufficient period of time has elapsed to evaluate the growth of those children who have had the more corrective operation of pulmonary valvulotomy.

## CONCLUSIONS

1. Growth studies, using the Wetzel Grid, have been carried out on patients with the tetralogy of Fallot.

2. Growth data were available on sixty-six patients who had not yet had surgery. Study of their growth as a group showed that a majority did not have good physiques although a majority were not of very poor physique. As a group their speed of growth was considerably slower than might be expected in the general population.

3. Twenty controls not operated upon were individually studied and the majority were found to lose speed of growth over time. Contrariwise a majority of this group did not develop a more poor physique over time.

4. Forty-seven patients were operated upon and their growth individually compared postoperatively with the preoperative pattern. There was no constancy in their patterns, but almost one-half of them continued to lose in growth speed and likewise almost one-half developed more poor physiques postoperatively than they had preoperatively. There was no correlation between success of the operation as measured in terms of exercise ability and subsequent growth.

5. Among the controls there was no correlation between gain or loss in growth speed or physique over time and exercise ability.

6. Possible factors influencing growth in children with congenital cyanotic heart disease were discussed.

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# PRIMARY CARCINOMA OF THE LIVER IN A BOY AGED 20 MONTHS

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DESPITE the relative rarity, primary carcinoma of the liver is not an uncommon cause of hepatic tumor in infants, and to a lesser degree in childhood. However, because of the infrequent diagnosis of this condition except at autopsy or by exploratory operation, it seems worth while to report an additional case in a 20-month-old boy, determined at post mortem. Steiner[1] reviewed the literature in 1938 and added two cases of his own. The total was seventy-seven under 16 years of age. Since then, twelve additional cases have been reported.[2-10] Of these eighty-nine cases and the one of our own, forty-seven, or 52.2 per cent, were 2 years of age or younger.

## CASE REPORT

*Clinical History.*—A 20-month-old boy was admitted to the Pediatric Service on Feb. 11, 1951, because of pallor, loss of weight, and constipation of about two months' duration. An enlargement of the abdomen had been noted for about two weeks.

On admission the patient appeared chronically ill, and weighed 9.5 kilo (20½ pounds). His face had very little expression. There was a decided pallor to the skin and mucous membranes but no icterus. The heart and lungs were normal except for a few scattered râles in the right chest. The abdomen was protuberant; the skin over it was thin and the superficial veins prominent. On the right side a firm, smooth mass extended to or beyond the mid-abdominal line and to the level of the pelvic crest. This mass was slightly movable by bimanual palpation. By rectal examination, the presenting edge was rounded, firm, and smooth.

*Laboratory Data.*—Red blood count was 2.7 million; color index 0.7; urine negative. X-ray of the chest showed areas of increased density consistent with early metastases in the right middle lobe and left upper field. X-rays of the skull and long bones were normal. An intravenous pyelogram revealed a normal left kidney. The right kidney was not well outlined because of the overlying shadow.

A diagnosis of Wilms' tumor was made. This diagnosis was concurred in by a member of the urological staff and the consulting oncologist.

*Clinical Course.*—In view of the x-ray findings of metastases in the lungs it was felt that an operation to remove the tumor was not warranted. Deep x-ray therapy was recommended to reduce the size of the tumor to afford the patient more comfort. Blood transfusions were given for supportive measures. The tumor proved to possess a high degree of radiosensitivity in the doses used. Because of the favorable response to the tumor mass, a trial dose of radiation was made on the right lung. These metastatic areas regressed very decidedly. Later the left lung was radiated. The patient improved in general well-being; his appetite returned and he was a happy child about the ward. On July 27 he was discharged to a foster parent. He was followed in the X-ray Department for therapy. His progress was reported satisfactory until October 14 when suddenly, while playing with some toys in the home, he cried out, vomited, and was found in a state of shock. He was described as pulseless and cold. His breathing was dyspneic, and he could not be aroused.

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He was readmitted to the hospital. His temperature was 105° F. There was twitching of the right side of the face and left-sided convulsions. About twelve hours later he developed left-sided paralysis. His condition improved somewhat, but the left side remained weak. He was discharged on October 30 at the convenience of the foster parents. He was readmitted on November 21 because of progressive respiratory difficulty, restlessness, and increasing drowsiness. He had jaundice at this time. The abdominal tumor had again increased in size. His breathing was dyspneic, and his chest was dull to percussion and filled with coarse, moist râles. The patient died on Nov. 28, 1951, eight months after the first admission.

Fig. 1.—Cut surface of liver, showing tumor tissue studded throughout the liver. Note large tumor masses projecting downward from right lobe.

*Autopsy Report* (Dr. Henry R. Muller).—The peritoneal cavity contained 500 c.c. of bloody fluid. The liver edge extended down to the umbilicus. The intestinal tract, kidneys, spleen, pancreas, and the adrenal glands were normal. The liver weighed 1,400 grams. It was studded with numerous large nodules on the surface. One very large mass projected downward from the right lobe. Two small nodules on the surface of the left lobe had fresh red blood around them and seemed to be the nodules responsible for the hemorrhage. Between the nodules and masses, areas of liver tissue had a yellowish brown tinge. The cut surface of the liver presented soft nodules, some hemorrhagic, scattered throughout the liver. No lymph nodes were present in the abdominal cavity.

Thorax: No free fluid was found in either pleural cavity. Heart was in normal position.

Lungs: Nodules up to 1½ cm. were scattered throughout both lungs—some of them hemorrhagic. There was considerable uninvolved lung tissue which had a yellow tinge.

Head: Scalp, skull, and dura were normal. The brain showed signs of intracranial pressure with convolutions on both sides flattened. It

weighed 960 grams. In the posterior portion of the right occipital lobe there was a large (5 cm.) brown area occupied by a nodule of neoplasm surrounded by blood, fluid, and clotted blood. In the anterior portion of the left frontal lobe there was a 1½ cm. area of metastasis with blood around it.

*Microscopic.*—

Liver: The tumor nodules were composed of small, undifferentiated embryonal cells arranged in sheets and also in small glandular or acinar structures. There were many small rosette structures with embryonal cells radiating from a small central lumen. Also larger glandular structures formed by a single layer of these cells were present. The veins were filled with plugs of neoplasm, which explained the neoplasm's extensive spread through the liver and metastases in the lung and brain. The cells contained numerous vacuoles of fat.

Brain: Here the metastases showed cells more differentiated and an attempt made to form liver cords. Bile capillaries contained plugs of bile, and many cells had small vacuoles of fat.

Lung: As in the brain, the metastases had embryonic cells as well as more differentiated cells resembling liver cells. These contained small plugs of bile in capillaries and many vacuoles. In sections stained with scarlet R, the vacuoles stained for fat. The same staining of fat was obtained in the liver cells. Kidney, spleen, and adrenals were normal.

*Remarks.*—This is a primary hepatoma with embryonic cells in the liver and with embryonic and more differentiated tumor cells in the metastases of lung and brain. These differentiated cells had bile capillaries containing plugs of bile as well as globules similar to those in the liver itself. Scarlet R stain showed these globules to have been occupied by fat.

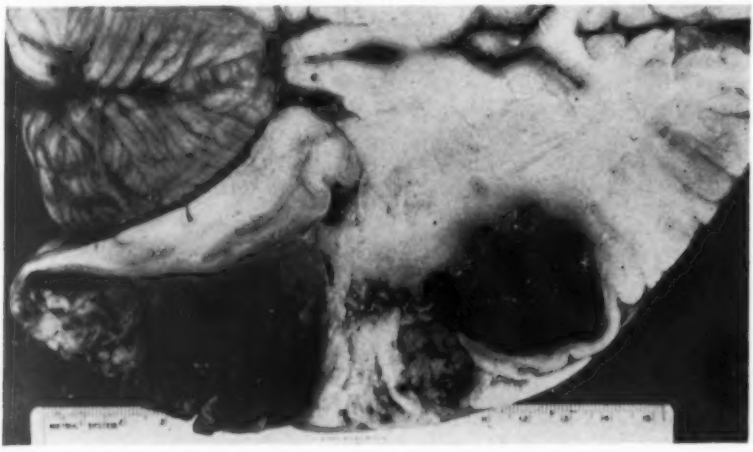

Fig. 2.—Cut section of brain, showing multiple areas of metastases and hemorrhage.

*Pathological Diagnoses.*—Primary malignant hepatoma with metastases to lungs and brain. Fatty liver.

## COMMENT

The diagnosis of kidney tumor seemed the most likely at the time of admission. The response of the tumor to radiation was also compatible with this type of tumor. However, a primary carcinoma of the liver in this age group should have been considered, especially when the tumor was in the

location described. Metastases to the lungs are reported in 27 per cent of cases brought to autopsy. In reviewing the available literature, I was unable to find a report of metastasis to the brain. The acute hemorrhage into these metastatic areas probably coincided with the patient's collapse on November 21.

SUMMARY

A case of primary carcinoma of the liver (hepatoma) with metastases to the lungs and brain in a 20-month-old boy who lived eight months after admission is reported. This case makes a total of ninty to be reported. Of these, forty-seven, or 52.2 per cent, are under 2 years of age.

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# JUVENILE CIRRHOSIS OF THE LIVER

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CIRRHOSIS of the liver is rare in childhood. Of a total of about 83,000 admissions to a St. Louis children's hospital[1] there were only eleven proved cases of portal cirrhosis. The familial tendency of these cases is known but the etiology is often obscure. The pathologic and clinical classifications seem still not clearly defined. In view of these facts it was felt that it would be desirable to report an additional case of juvenile cirrhosis with emphasis on its familial tendency, pathology, and possible etiology.

## CASE REPORT

M. A. Mc., a 15-year-old white female, kindly referred to me by Dr. Margaret Dowell, was first seen in October, 1951, with chief complaints of (1) big, uncomfortable abdomen; (2) sore throat for two days; and (3) tiredness.

*Present Illness.*—She was well until 6 years of age when, without obvious cause, she became listless, and her mother thought she passed bloody urine for three weeks. There was no edema. She is said to have become anemic.

After six weeks she seemed well until age 9½ when she had gradual onset of generalized edema with jaundice, both symptoms lasting about a month. Various urinalyses, according to the hospital record of this illness, showed specific gravity ranging from 1.019 to 1.029; albumin ranging from 1 plus to faint trace, microscopic showed usually 10 to 12 white blood cells and 1 to 2 red blood cells per high-power field. Hemoglobin was 8.0 grams; red blood count 2,690,000; white blood count normal. Icterus index was 30. Blood urea nitrogen was 14.5 mg. per cent. She had had a temperature of 100° or 99° F. almost every day.

During the remainder of this year she required abdominal paracentesis on a number of occasions. Studies abstracted from hospital records of June, 1947, showed: urine, no albumin; a few white blood cells and red blood cells per high-power field; blood pressure 100/70; blood urea nitrogen 11.0 mg. per cent; sedimentation rate 40 mm. in 60 minutes. Later in June she was studied in a pediatric hospital in a neighboring city and the pertinent findings were as follows: blood serology negative; *blood type 3B, Rh positive;* hemoglobin 13.1 grams; red blood count 3,600,000; white blood count 20,700, with 78 per cent polymorphonuclears, 20 per cent monocytes, 2 per cent staff cells; sedimentation rate 16 mm. in 45 minutes. Urinalysis showed "some albumin in practically every specimen"; occasional red blood cells, and occasional white blood cells. Blood urea nitrogen was 7.0 mg. per cent; serum albumin 2.4 grams; globulin 1.5 grams. Excretory urogram was essentially normal. Final diagnosis at this hospital was "chronic glomerulonephritis."

She required abdominal paracenteses several times in the autumn of 1947. In January, 1948, she was admitted to a hospital for abdominal pain. She showed fever up to 100.4° F. Urinalysis and complete blood count were essentially normal.

She has had during these years four respiratory infections which have been diagnosed as pneumonia.

When first seen in October, 1951, she had been ill for about two weeks with weakness, swelling of the abdomen, and a mild upper respiratory infection.

Address: 1280 Center St.

*Family History.*—Mother and father are living and well. There is no known history of jaundice in the family. The mother has had no miscarriages. The mother's blood is *3B, Rh negative;* Rh antibody titers study on her blood April 28, 1952, was reported as showing no agglutinating antibody titer and no blocking antibody titer. She states that neither of her two children had any jaundice, anemia, or other evidence of abnormality in the first year of life. No vermifuge has ever been given to either child. The parents do not use alcohol. The patient had only one sibling, who died at age 15 years with a diagnosis of "acute glomerulonephritis." Review of his chart shows that about two weeks after an upper respiratory infection he had an illness characterized by liver enlargement, jaundice, gross ascites, and anemia. Urinalyses showed 1 plus albumin, from 40 to 10 white blood cells per high-power field, and from 50 to 25 red blood cells per high power-field. Hemoglobin was 7.0 grams; red blood count 1,191,000; Kahn negative; no blood typing done; blood urea nitrogen March 3, 1939, was 15.5 mg. per cent; icterus index on March 3 was 5. There was no test on March 26, but nurses' notes state "markedly jaundiced." He died after twelve hours in stupor on March 26, 1939. No necropsy. The course seemed characteristic of nodular cirrhosis in a terminal phase.

*Physical Examination.*—The temperature was 98° F.; blood pressure 110/70; normal weight 125 pounds, presenting weight 137½ pounds; retinas normal; abdomen, gross ascites.

*Laboratory Studies.*—Urinalyses were normal. Red cell fragility test was normal; complete blood count within normal limits; blood urea nitrogen 16.0 mg. per cent; blood creatinine 0.94 mg. per cent; blood cholesterol 262 mg. per cent; blood chloride 454 mg. per cent. Total blood protein was 7.0 grams per 100 c.c., albumin 3.1 grams, globulin 3.9 grams. Bromsulfalein test (300 mg. dye); 5 minutes, 16.5 per cent retained; 30 minutes, 10.3 per cent retained. Thymol turbidity 5 units. Alkaline phosphatase 18.1 units (normal 2 to 9).

*Course.*—Diuresis occurred spontaneously with loss of 12½ pounds in fourteen days, and soon a large spleen, down to the anterior superior iliac spine, could be palpated. The liver seemed small to percussion. X-ray studies, employing the method described by Zelman[2] (air contrast enema plus Seidlitz powder distention of the stomach), showed the large spleen and a quite small liver (Fig. 1).

Fig. 1.—Flat plate abdomen in upright position, showing large spleen and atrophic liver outlined by gas in colon and stomach.

*Diagnosis.*—Nodular cirrhosis of the liver.

*Further Course.*—The patient did poorly. She showed varying degrees of jaundice. Later she exhibited vascular spiders, increasing ascites, and varying pleural effusion. She expired April 7, 1952, after a period of two weeks of gradually increasing semistupor. Total course from onset was nine years.

*Necropsy* (Dr. W. L. Lidbeck).—Principal findings were limited to the spleen and liver. The kidneys were

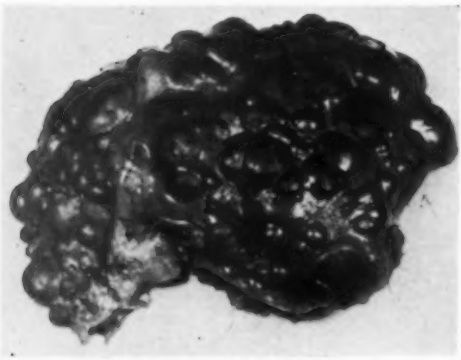

Fig. 2.—Gross appearance of the liver showing atrophy and large regenerated nodules separated by coarse fibrous bands.

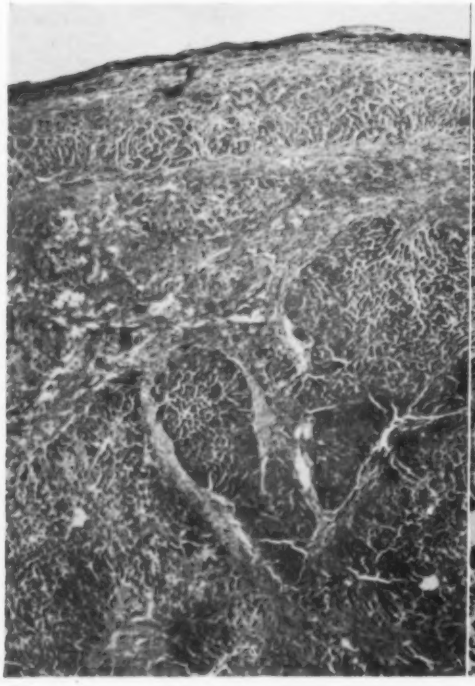

Fig. 3.

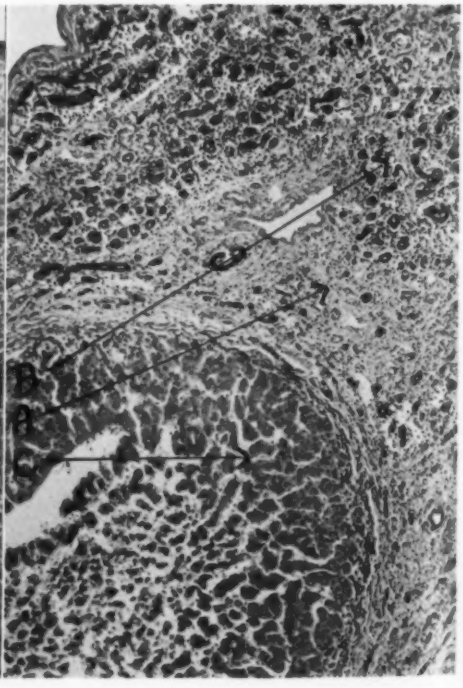


Fig. 4.

Fig. 3.—Low-power microscopic section of liver showing general architecture.

Fig. 4.—Medium-power microscopic section of liver showing heavy fibrous tissue (*A*) with proliferated bile ducts (*B*) and a nodule of regenerated liver cells (*C*).

grossly normal. The spleen weighed 420 grams. The capsule was thin; cut surface flat, firm, and of uniform dark color. The liver was markedly atrophic, weighing 640 grams, and showing extensive and extremely coarse nodularity and lobulation (Fig. 2). The liver was firm and greenish yellow to dark brown. The gall bladder contained a small bile pigment stone.

*Microscopic.*—

"*Liver:* Sections from various parts of the liver (Figs. 3 and 4) are examined and the lobular pattern is greatly distorted. These structures vary markedly in size and in many it is difficult to identify the central veins. Between the lobulae extend bands of dense fibrous tissue in which there is a moderate degree of lymphocytic infiltration. Such areas also contain large numbers of bile ducts. Occasional small nests of hepatic cells are found in the fibrotic areas suggesting an attempt at liver cell regeneration. The cells comprising the lobulae are arranged in the usual cord-like manner but frequently the nuclei are enlarged and in most of these cells an abundance of granular brown pigment is found in the cytoplasm. Some of the cells are swollen and pale staining and the nuclei are less distinct than normal. Occasional bile thrombi are found within the canaliculi.

"*Kidney:* Sections of each kidney are examined. Some of the tubules contain hyaline or granular casts and some of them are deep brown in color suggesting bile staining. The tubular epithelium is somewhat swollen and granular.

"*Spleen:* There is pronounced increase in the reticulo-endothelial cells with marked reduction in the number of lymphocytes. These cells are spindle shape and their nuclei are closely arranged so that in some areas a fairly solid pattern is presented. Thickening of the walls of the arterioles is noted and there is some degree of hyaline degeneration."

There were no other abnormalities of note seen.

"*Necropsy Diagnosis.*—(1) Portal cirrhosis; (2) slight ascites; (3) generalized icterus, marked; (4) chronic cholecystitis with cholelithiasis; (5) splenomegalia; (6) acute passive congestion of the liver and kidneys."

## COMMENT

The history and course of this case suggest that recurring episodes of hepatitis perhaps were precipitated at times by acute upper respiratory infections. Recurring hepatitis may have led to searring and regeneration in varying degrees, eventuating in liver failure and death in cholemia.[3] It seems probable that pathologically the lesion resembled the cirrhosis following infectious hepatitis described by Kunkel and Labby.[4] This case, like their cases, showed large and small nodules of regenerated liver cells with a varying amount of fibrous tissue in different areas.

The use of special x-ray technique seemed valuable to demonstrate the size of the liver and the spleen.

It seems evident that the patient's only brother also died of nodular cirrhosis. The familial tendency in these cases is prominent.[5-9] A remarkable example of this nature is contained in the report of Schindler and Kindschi[10] describing cirrhosis of the liver in three brothers, each of whom died at 14 years of age.

The possible relationship of erythroblastosis has been mentioned by Keller and Nute[1] who state, "From our studies we have arrived at the conclusion that many cases of juvenile cirrhosis may be a part of, or the end result of, fetal erythroblastosis." Some support for this view may possibly be suggested by the Rh factor relationship of our case. However, an extensive study of cirrhosis following erythroblastosis[11] suggests that this form must be largely limited to the earliest years of life and probably frank erythroblastosis would be readily recognized at birth.

SUMMARY

1. A case of juvenile nodular cirrhosis of the liver confirmed at necropsy is reported. The patient's only sibling also died at the same age of the same disorder.

2. X-ray studies by the Zelman technique revealed the atrophic liver and enlarged spleen.

3. Possible relationship to recurrent hepatitis or to erythroblastosis is mentioned.

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# RECURRENT INTUSSUSCEPTION OF THE JEJUNUM

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THE following case warrants a report because of the unusual location, etiology, and chronicity of the intussusception.

K. H., a 3-year-old white female, entered the hospital June 15, 1951, with the history of vomiting and colicky abdominal pain of three days' duration. The parents had noted similar, less severe episodes during the preceding three months which disappeared spontaneously. Physical examination during one of the attacks was negative. The present episode was of longer duration than the previous attacks; the vomiting was more protracted and the periodicity of the pain more pronounced.

Examination on entry revealed a well-nourished, alert, mildly dehydrated child complaining of occasional abdominal pain. The abdomen was soft and no tenderness or masses were noted. The dehydration was corrected with parenteral fluids followed by apparent recovery. The gastrointestinal series, barium enema, blood count, and urinalysis were all reported as normal at this time.

The child was discharged on June 18, 1951, only to re-enter in three weeks with the same complaints but of greater severity. The bowel movements were at all times normal. She was markedly dehydrated, and everything taken by mouth was vomited. Examination at this time revealed a sausage-shaped mass in the left upper quadrant measuring approximately 5 × 1½ inches. A flat x-ray plate of the abdomen revealed a dense mass in the left upper quadrant displacing the descending colon medially. Barium enema was normal. The patient was thought to have a bowel obstruction probably proximal to the cecum. Surgical exploration of the abdomen was advised.

The abdomen was opened by an upper left paramedian incision and an intussuscepted mass was seen in the left upper quadrant approximately 8 inches in length. This mass was mechanically reduced and was found to be composed of about 36 inches of jejunum. After reduction a small pedunculated polyp was palpated at the lead point of the intussusception. The polyp was excised by a longitudinal incision of the bowel wall, which was then sutured transversely in two layers. The postoperative course was uneventful and she was discharged eight days following surgery. The pathologist reported the specimen as being a benign adenomatous polyp.

A review of the initial gastrointestinal series revealed a mid-jejunal filling defect (see Fig. 1).

Three weeks later the patient returned with the complaints of vomiting and progressive abdominal distention of twenty-four hours' duration. The abdomen was moderately distended, particularly in the upper quadrants, and somewhat tense and tympanitic. Rushes of peristaltic sounds could be heard in the upper abdomen, while the lower abdomen was silent. X-ray of the abdomen revealed marked gastric dilatation (see Fig. 2). A diagnosis of upper intestinal obstruction was made.

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The opinions and views set forth are those of the authors and are not to be considered as reflecting the policies of the Navy Department.

Fig. 1.—Lateral view of abdomen. Note the filling defect in the mid-jejunum. Film taken during the initial entry.

Fig. 2.—Anteroposterior view of abdomen. Third entry. Marked gastric dilatation of stomach. Note the small amount of gas distal to the stomach.

At surgery a stenotic area was noted at the site of polypectomy along with a constricting, adhesive band. This area was resected and an end-to-end anastamosis of the jejunum was performed. The lumen of the excised stenotic portion was found to be approximately one millimeter in diameter.

The patient recovered promptly and was asymptomatic for eight months. However, at this time the child again returned presenting the picture of a small bowel obstruction. She was explored for a third time and was found to have an adhesive band completely obstructing the jejunum several inches distal to the polypectomy site. The band was released, followed by an uneventful recovery.

## DISCUSSION

A review of the literature reveals a paucity of reported cases of (1) jejunal intussusception, (2) a causative factor in cases of intussusception, and (3) the rarity of tumors of the small intestine.

Kahle[1] analyzed 151 cases of intussusception over a thirty-four-year period and noted only one jejunal type, this being a post-mortem finding. Gibbs and Sutton[2] reviewed ninety-two cases without finding a case of jejunal intussusception, while Smith[3] and Hogg and Donovan[4] recorded one case each in their respective series of thirty-five and 123 cases. In the 610 cases reviewed at Boston Children's Hospital, Gross and Ware[5] found the following locations of the intussuscepted bowel.

| | |
|---|---|
| Iliocolic | 76.0% |
| Ilio-ilial colic | 14.0% |
| Jejuno-ileal or ileo-ileal | 5.0% |
| Colocolic | 2.1% |
| Multiple | 0.7% |
| Type not stated | 2.2% |

The finding of an etiology is itself unusual. In the above cases reviewed by Gross and Ware[5] no cause for the intussusception could be found in 95 per cent of the cases. Ravitch and McCune,[6] although not reporting any jejunal intussusception in their series of 151 cases, noted that in nine cases of recurrent attacks of intussusception, three of these children were found to have polyps at operation. They suggest that intestinal polyps be considered whenever there is a history of previous attacks. Williams and Williams[7] reported two cases of adenoma of the small bowel producing intussusception, while Jeghers and associates[8] found ten cases of intussusception due to polyps. Jeghers and associates noted the familial trend of melanin spots of the oral mucosa, lips, and digits, intestinal polyps, and intussusception.

The presence of a tumor (malignant or benign) in the small bowel is also rare. Raiford[9] could find only fifty benign tumors of the small intestine in the material of 11,500 autopsies and in 45,000 surgical pathological specimens at the Johns Hopkins Hospital. Ladd and Gross[10] found one case of jejunal polyps in a series of ninety-two cases of alimentary tract polyps. Rankin and Newell[11] reported only thirty-five cases from the records of the Mayo Clinic. Raiford listed as causes of the relative infrequence of tumors in the small bowel (1) the relative freedom of stasis of the small intestine (except in the terminal portion of the ileum, where the incidence of tumors is highest) and (2) the fact that there is little chance for arrested development and misplaced embryonal tissue in the small intestine because it develops chiefly during the last four months of fetal life.

## SUMMARY

A case is reported of a 3-year-old girl with recurrent attacks of intestinal obstruction who was found to have a jejunojejunal intussusception caused by a benign adenomatous polyp.

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# Medical Progress

## THE NEWBORN INFANT

### An Interpretative Review

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THE newborn infant, his unique anatomic and physiologic characteristics, the dramatic adjustments of the neonatal period, and the problems that may be encountered have received an unusual amount of attention recently. This is reflected in the increasing number of articles dealing with the newborn infant in medical periodicals. All have been interesting, many have added significant new facts, and some have contributed information that has real value in everyday clinical practice. Any attempt to critically review all of this would be presumptuous. In the following pages I shall only try to indicate what seem to me to be the significant trends and evaluate the application of the newer knowledge in clinical practice.

### I. THE IMPORTANCE OF THE PRENATAL PERIOD

Greater appreciation of the importance of embryonic and fetal growth and development in determining the status of the infant at birth is one of the most significant trends. Emphasis on the normal anatomic and physiologic characteristics of the fetus is found in the writings of Windle,[1] Barcroft,[2] Smith,[3] and Potter,[4] for example. An important concept takes form from these studies. This is that fetal growth is concerned with two goals, that of maturation of organs and tissues according to a predetermined pattern in preparation for postnatal function, and that of maintaining a physiologic setup attuned to the conditions of intrauterine environment but which gradually changes toward the end of gestation in preparation for the environment of life outside the uterus.

Fetal preparation for extrauterine respiration is shown in the development of the pulmonary alveoli so beautifully demonstrated by Potter.[4] The significant fact in her careful histologic studies of the lungs of fetuses at various gestational stages was the continually increasing development of the capillaries in the alveolar septa with advancing fetal age. At term the septa consist almost entirely of capillary loops with only scattered epithelial cells. This is highly favorable to efficient gaseous exchange when air-breathing is initiated. The clinical importance of this knowledge in evaluating the status of the prematurely born infant is obvious. The more immature the infant and consequently the less advanced the capillary development in the alveolar septa, the less efficient will gaseous exchange be. In fact when premature birth occurs before a certain minimal stage of capillary development has been reached, gaseous exchange sufficient to maintain life may not be possible.

Fetal development of the central mechanism for control of respiratory activity has been discussed by Barcroft,[2] Potter,[4] and Keéri-Szántō and associates.[5] Apparently the earliest or primitive respiratory center is in the first cervical segment of the cord; this is a reflex center responding to afferent sensory stimuli. Cephalad to this there develop three other centers with inhibitory and regulatory properties each in succession at a higher level with advancing gestational age. The earliest fetal respiratory movements are purely the result of direct muscular stimulation, later they are simple sensory-motor reflexes, and still later with the development of inhibitory control they are produced by depression of this inhibitory mechanism through interference with the blood supply from the placenta. There is no longer any doubt of the occurrence of intrauterine respiratory movements. They probably occur usually as a result of some degree of fetal distress. But their occurrence is an indication of fetal preparation for neonatal respiratory function.

The continuing development of the kidneys morphologically has been shown by Potter.[6] Nephrogenic zones were found in the kidneys of fetuses up to about the thirty-fifth week of gestational age. She demonstrated that nephrogenesis continues to that age even when fetal life is interrupted by premature birth before the thirty-fifth week. Likewise, gradual and continuing maturation of renal function has been shown in the studies comparing the functional capabilities of the kidneys of premature infants with full-term newborn infants and with infants beyond the newborn period.[7, 8, 9, 10, 11]

In like manner the progressive functional maturation of the liver has been demonstrated by the studies of Davidson and associates[12] and Fashema.[13] And other tissues and organs mature morphologically and in functional capacity with advancing fetal age.

All of this has greatly increased our understanding of the physiology of the newborn infant in which there is a merging of fetal physiologic characteristics with those resulting from conditions imposed by the new manner of life after birth. It has a bearing also on our interpretation of pathologic conditions arising from the insults of the birth process and from other causes in the neonatal period.

The effect upon the embryo and fetus of unfavorable intrauterine environment has received attention from many angles. Through the studies of Gregg,[14] Warkany and co-workers,[15-17] Ingalls and associates,[18] Worcester and associates,[19] Fraser and Fainstal,[20, 21] Smith,[22] Antonov,[23] Barcroft,[2] Wilson,[24] and others, the importance of maternal health to the welfare of the offspring has been emphasized.

Gregg's clinical studies[14] demonstrated that rubella in the first trimester of pregnancy will in a high percentage of cases result in malformations in the offspring. There has been confirmation of this from subsequent studies by others. Suspicion has been cast on other viral diseases but as yet no real proof is at hand. Warkany and co-workers[15-17, 24] were able to show in experimental animals that maternal depletion of a specific nutritional factor results in specific congenital anomalies in the offspring. Rats whose mothers had been deprived of riboflavin had such skeletal deformities as cleft palate, syndactylism,

fusion of the ribs, and shortening of the jaw and of bones of the forearms and legs. When there was deprivation of vitamin A, malformations occurred, essentially, of the soft tissue structures, the eyes, heart, diaphragm, kidneys, and other urogenital organs.

Ingalls, Curley, and Prindle,[18] working on the hypothesis suggested by clinical studies, that mongolism and perhaps tracheo-esophageal fistula and retrolental fibroplasia were due to anoxia at critical stages of fetal development, subjected pregnant mice to rarefied atmospheres at various periods after conception. Their results indicated that malformations such as anencephaly and cleft palate could be produced by maternal anoxia, that the effect upon the fetus varies with the degree of anoxia and the stage of gestation in which the anoxic insult occurs, and upon the anatomic characteristics of the site at which localized cellular damage occurs, rapidly differentiating tissues being most vulnerable.

Further evidence of the effect of environmental factors, in particular of endocrine factors, on the developing embryo comes from the recent experimental studies of Fraser and Fainstal.[20] Cortisone was injected into pregnant mice and malformations in the offspring were produced. The incidence of the malformations was found to vary with the genetic constitution of the treated mice, the dosage of cortisone used, and the gestational stage at which treatment was begun.

Conclusions regarding the etiology of congenital malformations have been summarized by Warkany[17] and by Fraser and Fainstal[21] essentially as follows. Some defects are genetic in origin, some are due to environmental factors, and others result from an interaction between genetic and environmental influences. "Normal development depends upon a sound inheritance as well as upon proper environment. Either a defective gene or defective supply of nutritional elements from the mother may result in embryonic malformation or death" (Warkany). And to this statement we can add, changes in environment produced by some maternal infections and possibly severe disturbance of maternal endocrine balance.

The practical implications of these clinical and experimental studies are: (1) They prove that at least some congenital anomalies are not completely beyond the possibility of control; (2) they dispel some of the mystery of malformations in cases where no hereditary taint is apparent and this is valuable to the physician called upon to discuss the matter with the parents of a malformed child; and (3) they sharply emphasize a vital relationship between the mother's health and the development of her offspring.

The effect of maternal diet upon fetal growth has been further substantiated by recent studies. Smith's[22] analysis of the infants born in Amsterdam and Rotterdam during the period of the severe dietary restrictions imposed during German occupation and in that after liberation, and the studies of Antonov[23] in Leningrad during the prolonged siege of that city confirmed the earlier findings of Ebbs, Tisdall, and Scott[25] and of Burke, Harding, and Stuart.[26] Severe restrictions of maternal food intake result in a significant decrease in the stature and weight of the infant at birth. Smith's[22] studies seemed also

to confirm that in man, as had been so clearly shown by Barcroft[2] in sheep, this effect upon the offspring occurred largely if not solely when maternal dietary restrictions were imposed during the latter half of pregnancy.

Qualitatively, as well as quantitatively, the nutritional requirements of the mother must be adequate in order to meet the full needs of the fetus. This is indicated by the studies of Hamil and collaborators[27, 28] and Slobody and associates[29, 30] in regard to vitamins of the B complex and vitamin C, and of Boder[31] in regard to vitamin D. Higher levels of vitamins of the B complex and of vitamin C were found in the cord blood than in the maternal blood and there was found excessive excretion of these vitamins in the urine with a gradual reduction of the blood levels in the first three to five postnatal days. Slobody[30] found this to be true of vitamin C in premature as well as in term infants. The conclusion would appear to be that the physiologic processes of intrauterine life require a greater concentration of these vitamins in the tissues than do the physiologic process under the changed conditions after birth. During intrauterine life these vitamins seem to be retained by the fetus for his needs even though the maternal blood level is reduced below the mother's requirements. The necessity of adequate fortification of the maternal diet with these vitamins is implied. Boder[31] found in her study of a very large number of newborn infants that there was a highly significant inverse relationship in the incidence of congenital cranial osteoporosis (physiologic craniotabes) and the amount of sunshine available during the latter months of pregnancy. This strongly suggests that maternal vitamin D inadequacy has an effect upon the calcium metabolism of the fetus.

It has long been recognized that fetal health could be and often was disturbed by maternal disease, chronic or acute and metabolic or infectious; also that certain infectious diseases are transplacentally imparted to the fetus. We need only call attention to the fact in order to emphasize the importance of a careful prenatal history in evaluating the status of the newborn infant. Special mention should, however, be made of a few conditions that have received special attention recently.

*Diabetes.*—The status of the offspring of the diabetic mother is of particular interest. It constitutes a problem of relatively recent origin. Control of diabetes with insulin made childbearing possible and the number of newborn infants presenting this problem has continued to increase. Among them there is a high neonatal mortality and a high incidence of premature birth. At first it was felt that hypoglycemia resulting from hyperinsulinism was their principal problem. They frequently had very low blood sugar levels and at autopsy hyperplasia and hypertrophy of islands of Langerhans were found. More recent investigations indicate that hypoglycemia in itself is probably seldom the cause of neonatal death. Low blood sugar levels are characteristic of normal newborn infants in the early postnatal days and even extremely low levels are not accompanied by clinical symptoms.[32, 33] The work of Priscilla White[34] has indicated that the offending factor may be an endocrine one, characterized by a depression of estrogens. This explanation has been chal-

lenged by some, but White's[34] reported results are quite convincing. She reports a marked reduction in neonatal mortality and in the incidence of premature births by the use of replacement therapy in a large group of pregnant diabetic women whose estrogens were found to be low, as compared to similar groups not so treated. It is, at any rate, quite clear that the problem of the offspring of the diabetic mother is more complex than the mere overproduction of insulin by the fetal pancreas compensatory to the hyperglycemic fetal environment. It seems reasonable to presume that the general endocrine imbalance of a diabetic woman further disturbed by the endocrine changes of pregnancy might profoundly influence the intrauterine environment and alter the physiologic processes of her fetus in a variety of ways.

Some interesting features that have been commented upon are: higher than average birth weight due probably to the maternal hyperglycemia, a higher than usual erythroblast count in the circulating blood, at autopsy many extramedullary centers of hemopoiesis in the liver and spleen, and in addition an enlarged heart. Frequently abnormalities of the placenta have been noted.

Miller[35] and others have noted these findings in some infants of mothers who were not diabetic. They have assembled statistics on these cases which they claim indicate a high percentage of these mothers were prediabetic and later had clinical diabetes. Evidence so far presented is not convincing, but is suggestive.

It is apparent that knowledge in this field is still incomplete. In the meantime certain methods of intelligent care are suggested by the facts at hand —prenatally, adequate control of the diabetes and substitution therapy when indicated as suggested by White[34]; natally, wise selection of type of delivery, administration of oxygen in surgical deliveries, and restriction of sedatives; postnatally, administration of oxygen and restriction of fluids in the first two to three days. Whether administration of glucose and the use of epinephrine to prevent hypoglycemia or to treat it if present is indicated or not is an unsettled question.

*Congenital toxoplasmosis* is caused by transplacental transfer of the protozoa from an actively infected mother to her fetus. The principal damage is in the central nervous system and the eyes. Evidence of cerebral pathology and of chorioretinopathy, and later areas of calcification in the brain demonstrated by roentgenograms are the cardinal findings. The studies of Sabin[36] and his co-workers indicate that infection with Toxoplasma is quite common in the general population of certain sections of the country. Fortunately, infection of the fetus seems to occur only when maternal infection is active and the chances of this being the case are not great. From a practical standpoint the most significant clinical information that has come from the studies of Sabin and his group[36] is that analysis of data on proved cases of congential toxoplasmosis indicates that subsequent children born after the Toxoplasma-infected child are normal. The importance of this knowledge to the physician, called upon to advise parents on the advisability of having other children, is obvious.

*Endocardial sclerosis* and endocardial fibroelastosis are names now used

to designate a condition previously considered to be fetal endocarditis. The pathologic characteristics are cardiac hypertrophy, involving chiefly the left ventricle, thickening, opacity and milky discoloration of the endocardium, and varying degrees of distortion of the cardiac valves. The antenatal process responsible for this condition is unknown, but there has been no evidence found to substantiate an infectious origin. It appears more likely that it is a congenital developmental defect in which endocardial fibrosis interferes with the emptying of the arteriolumenal capillaries resulting in changes in the myocardium with final cardiac failure. Death usually occurs within the early weeks after birth.[4, 37, 38] These conclusions seem to mark the exit of one more disease from the shrinking realm of fetal bacterial infections.

*Viral infections* of the fetus are, however, assuming greater importance. Congenital pneumonitis quite clearly due to maternal virus infection has been demonstrated by Adams,[39] and congenital viral hepatitis seems now to be a well-substantiated clinical entity.

*Erythroblastosis fetalis* will only be mentioned in this review although it rightfully belongs here in the category of diseases due to prenatal influences. The subject has been so exhaustively covered by authorities that nearly all who read these pages will be at least as familiar with its intricacies as I. Wider recognition and improved methods of treatment have resulted in a significant lowering of its mortality rate. Saving more lives has, however, brought in its wake an increasing number of infants handicapped by kernicterus, adding to the already serious problem of mentally retarded and cerebral spastic children. The pathogenesis of kernicterus is still not known. Zuelzer's[40] study indicates quite clearly that hemolytic disease is not the only condition which may result in kernicterus. The subject needs further study.

*Postmaturity and Placental Integrity.*—The importance of placental adequacy in regard to fetal gaseous exchange has recently been stressed, particularly by Clifford.[41] He called attention to the clinical and pathologic manifestations of prolonged intrauterine anoxia as it affects neonatal adjustments, and in most instances abnormal changes in the placenta were found which were of sufficient degree of severity to account for a protracted period of prenatal fetal anoxia. In the group studied there was a relatively large number of postmature infants, and the changes in the placentas appeared to be senile degenerative changes. More recently Clifford[42] has reported statistical data showing a significant upswing in the neonatal mortality rate in infants carried beyond term which increases with the degree of postmaturity. This emphasizes the importance of trying to find a more accurate and at the same time practical method of determining gestational age than we now have. Higher mortality rates among large infants is not a new observation, but the recent statistical report from New York City by Baumgartner and collaborators[43] is clear documentary evidence of the fact. It was possible to calculate "best birth weights" from their data. For male infants this was 3,000 grams, for females 2,880 grams. For whites it was 2,990 grams and for nonwhites 2,830 grams. While there are other factors

that may be concerned in making very large infants poorer risks, the implication is clear that relative maturity is more important than size in governing variations in death rate.

These observations seem to indicate that a definite hazard to the fetus accompanies postmaturity, probably associated with retrogressive or senile degenerative changes occurring in the placenta beyond term. This subject deserves serious study because, if true, general recognition of this hazard by obstetricians could significantly lower fetal and neonatal mortality rates.

### II. BIRTH AND NEONATAL ADJUSTMENTS

A considerable volume of knowledge relating to the physiology of the fetus, and of the newborn infant during the period of adjustment has accumulated in recent years. This has added greatly to our understanding of neonatal characteristics. It is easier to accept many of these peculiarities as normal phenomena when the basis for them is known, and the temptation to try to "correct" them by methods that amount to meddlesome interference is lessened. The very fact that all but a small fraction of the total number of infants born alive, particularly when born at term, make their neonatal adjustments successfully and smoothly should be proof that nature has made ample provision for this transition. But it is a satisfaction to have some idea of what is going on, ideas valuable in evaluating the occasional infant who experiences difficulties.

It will be impossible to review the studies on fetal and neonatal physiology in a thorough manner in this article. I can only refer to those which appear to me to be of special practical importance.

*Respiration and Respiratory Difficulties.*—Some progress has been made in clarifying the initiation of respiration after birth and in explaining types of respiration. The publications of Barcroft,[2] Wilson,[44] Smith,[45] Howard and Bauer,[46, 47] and Graham and coworkers[48] have been particularly helpful. Barcroft[2] from his studies of sheep concludes that respiration occurs when the sum total of stimulation from different sources is sufficient to overcome central inhibitions. Stimuli are chemical, from changed relationships between oxygen and carbon dioxide concentration at the respiratory center, and sensory, from afferent nerve impulses originating in the skin, mucous membranes, and muscles. These are augmented in an auxiliary manner by stimuli from the chemoreceptor mechanism of the carotid and aortic ganglia activated by relative anoxia. For this response an intact respiratory center is postulated; the responsiveness of the center is dependent upon adequate oxygen supply to the cells of the center.

Breathing of an immature type, i.e., variants of Cheyne-Stokes breathing, occurs in a high percentage of normal newborn infants in an atmosphere of air alone. Regular rhythm can be brought about by increasing the oxygen concentration.[46, 47] The majority of premature infants breathe while in an atmosphere of air as if suffering from oxygen-lack, yet do not have a strikingly reduced arterial oxygen saturation; nevertheless, administration of added oxygen corrects this type of breathing.[48] When oxygen is reduced to 12 per cent, breathing of the newborn infant becomes irregular in type and the minute volume is lowered; this is the opposite of the response which

occurs in adults. It has been suggested that this may be due to an anaerobic metabolism in the newborn infant and the type of breathing a physiologic process aimed at conserving $CO_2$. Oxygen and $CO_2$ are so intimately concerned with the regulation of respiration that they cannot easily be divorced, and irregular types of breathing may well be a physiologic effort to quantitate one gas with reference to the other rather than a pathologic response to an alteration in the concentration of either one.[47]

In interpreting the results of these studies from a practical standpoint, there are several variables to keep in mind. One is the state of anatomic maturation of the lungs of the particular infant in question,[4] another is the state of anatomic maturation of the central mechanism for control of respiration,[2, 5] and still another is the adequacy of physiologic function of such other organs and tissues as the kidneys, the endocrine glands, the capillaries, and others. Respiration is a complex bodily function interrelated to many others and can be understood only in the light of these interrelationships.

Most infants breathe spontaneously and immediately or with only slight delay and carry on adequately even though their respiratory rhythm is frequently irregular. The majority of those who experience some difficulty are relieved by oxygen administration. These are the infants whose respiratory centers have been depressed by a moderately severe degree of anoxia from various causes during their birth.

The infants who give us real concern are those whose respiratory center has been deeply depressed by severe anoxia of prenatal or natal origin, or by anatomical injury, and those with mechanical obstruction of the pulmonary airways. What helpful new information have we in regard to these?

The various causes of fetal and neonatal anoxia have been exhaustively discussed in a number of publications,[41, 45, 49] as have also the effects of anoxia,[4, 50-52] and are generally appreciated by obstetricians and pediatricians. It should be emphasized that the effects of anoxia are not confined to the mechanism of respiration but are widespread; perhaps most important is its effect upon the integrity of the capillaries. Damage may result from hemorrhages in many structures, the lungs, pleura, brain, meninges, and other tissues.

Of considerable clinical significance is intrauterine anoxia of relatively long duration. Clifford's studies of this condition were mentioned above in relation to placental changes in postmaturity. Other conditions such as erythroblastosis are also responsible for placental changes that cause intrauterine anoxia. The infant in addition to respiratory depression often has a characteristic golden yellow discoloration of the vernix and of the nails, and in some instances maceration of the skin. They often give the impression that though born alive they had barely escaped an intrauterine death. This clinical picture and its probable etiology has not heretofore been sufficiently stressed.

There has been a revival of interest in the etiology and the clinical and pathologic manifestations of various types of pulmonary obstructive lesions. Of these the hyaline membrane (vernix membrane, asphyxial membrane) has received the greatest amount of attention,[4, 53-57] particularly in regard to the

nature of the membrane and its origin. It is recognized that pulmonary hyaline membrane is a major factor in deaths from respiratory causes in the newborn period. The membrane is plastered against the walls of the respiratory bronchioles, the alveolar ducts, and the alveoli. The chief damage appears to result from plugging the alveolar ducts and producing secondary or resorption atelectasis. It occurs most frequently in premature infants. Among full-term infants it is found frequently in those born by cesarean section and in births associated with prenatal and natal anoxia. Analysis shows the membrane to be of protein material; vernix is not a constant component. The investigations of Blystad, Landing, and Smith[57] indicate that the concentrated protein is from amniotic fluid. Air-breathing of some duration seems to be essential for its formation. They did not find hyaline membranes in stillborn infants nor in infants dying within one hour after birth. That this may not be the only source of hyaline membrane is indicated by the studies of Miller.[53] He believes it to be a protein exudate from injured tissues of the bronchioles and alveoli. Others also have been unwilling to accept aspirated amniotic fluid as the only source of the concentrated protein of the membrane. Whatever its cause, hyaline membrane is a serious and a common cause of respiratory difficulty. The clinical picture is quite uniform. Breathing is usually quite normal for the first two or three hours after birth, then evidence of dyspnea appears, associated with retractions of the costal margins and lower sternum and with grunting. Cyanosis of varying degree develops. Death may occur within a few hours after the onset of symptoms in some cases while in others the condition may remain unchanged until the third or fourth day and then rather rapidly improve.

The subject of atelectasis was largely clarified by the careful studies of Wilson and Farber[58, 59] twenty years ago. Since then attention has been directed to associated pathologic conditions. Thanks to the Macklins,[60] the probable mechanism of the production of pulmonary interstitial emphysema, pneumomediastinum, and pneumothorax is recognized. Gumbiner and Cutler's[61] case reports and pathologic findings in pneumomediastinum were followed by others calling attention to this condition as a special hazard to the newborn infant. Recently Salmon, Forbes, and Davenport[62] reviewed six cases of airblock in newborn infants from the standpoint of the clinical, roentgenologic, and autopsy features. This comprehensive study emphasizes the fact that in the newborn infant with respiratory difficulty associated with atelectasis there are factors favorable to air-trapping which may lead to interstitial emphysema, pneumomediastinum, and pneumothorax. It is now becoming increasingly clear that atelectasis is usually a diffuse process. The obstruction is in many small bronchial radicles; some are completely obstructed from the first, many more become occluded after the alveoli have been inflated and give rise to secondary or resorption atelectasis when the air within the alveoli has been subsequently absorbed, while still other bronchial radicles are only partially obstructed, permitting air to enter the alveoli but hindering its exit. What we commonly speak of as atelectasis is rarely pure atelectasis, but rather a

combination of atelectasis and emphysema.

If this is the true picture it is obvious that, except in the rare instances of massive atelectasis due to obstruction of a large bronchus, no help can be expected from bronchoscopic aspiration. However, bronchoscopy, expertly done, as an aid in the treatment of asphyxiated newborn infants in the delivery room is quite another matter. Here removal of foreign material from the trachea and large bronchi by bronchoscopic technique can in some instances be a valuable measure both as an aid in resuscitation and in prevention of obstructive atelectasis. This deserves further consideration. One member of the delivery room personnel would need to be a properly trained and equipped bronchoscopist. There is need for serious consideration of a "delivery-room life-saving team" in every hospital with a large obstetrical department: a team composed of residents and nurses specially trained in the handling of all sorts of neonatal emergencies that occur in the delivery room. If bronchoscopy proves a valuable aid in neonatal emergencies, one member of such a team should be trained in that procedure.

Infants born by cesarean section present special problems. These have received considerable attention because the mortality in this group is high. In some instances the cause is, at least in part, related to the factors which made this type of delivery necessary, but in others this is obviously not the case. It has been suggested by Bloxsom[63] and others that passage through the birth canal in some way, not entirely clear, conditions the infant for normal respiratory function, and in birth by section the infant is robbed of this conditioning process. Landau and associates[64] have suggested that these infants suffer from shock probably because they are deprived of a significant quantity of blood due to the immediate severing of the cord at birth. Blystad, Landing, and Smith,[57] Gellis and collaborators,[65] and others have directed attention to an excessive amount of amniotic fluid in the respiratory tract and the stomach. Potter[4] also noted that at autopsy there was marked edema of the meninges, and more recently has reported that hyaline membrane is found in the lungs in a high percentage of cases. In the early management Gellis[65] has proposed aspiration of the fluid from the stomach immediately after birth and again one or more times in the next few hours. This is done to lessen the danger of regurgitated stomach contents being aspirated into the lungs. He reports a significant reduction in the incidence of respiratory difficulty and in mortality since this treatment was instituted. Many now advocate severe restriction of fluid intake in the first two to three days because of the greater tendency to edema in these infants. Oxygen administration should be accompanied by high humidity of the inspired air because of its possible influence in the prevention of hyaline membrane formation.

This subject is still not clearly understood. Until we know more about the physiologic changes and the physiodynamic factors involved in birth by section, and until we know more about how hyaline membranes are formed and how prevented, we will do well to follow the suggested methods of treatment given above, and urge that cesarean section deliveries be done only

after careful scrutiny of the indications.

It may be well at this point to make some comments about Bloxsom's Oxygen Air Lock. This device recently perfected by Bloxsom[66] was primarily conceived for infants delivered by section, on the theory that rhythmically applied alternating compression and decompression such as occurs in birth through the birth canal is essential to "condition" the infant for respiratory function after birth. It is now being used and recommended in some hospitals for all cases of asphyxia neonatorum. The asphyxiated infant is immediately placed naked in the warmed, humidified chamber containing an atmosphere maintained at 60 per cent oxygen concentration and the chamber locked. The pressure within the chamber is then raised to 3 pounds per square inch at which point an automatic trip mechanism allows the pressure to fall to 1 pound from which it is again raised automatically to 3 pounds. This cycle of alternating increased and decreased pressure is continued until respirations are regular and then the pressure is kept constantly at 2 pounds until all evidence of residual cyanosis in the hands and feet has disappeared. Following this the infant is placed in a regulation incubator supplied with oxygen at 60 per cent concentration. Some of the benefits claimed for this method of treatment are: that oxygen under pressure favors its absorption through the skin and mucous membranes; that by expansion of gases amniotic fluid and secretions are forced from the air passages; that alternating changes in pressure "condition" the infant for respiratory activity in a manner simulating that normally produced in passage through the birth canal; and that the infant is protected from the potential dangers of other methods of resuscitation. This is an ingenious device but there is not universal agreement that the physiologic premises on which it is based are sound. We must await the results of thorough trial and the opinions of many more observers than are now available before passing judgment on its merits. Asphyxia can result from many different factors and it would not appear likely that any single mechanical device would be indicated in all cases. Careful evaluation of the individual infant and intelligent selection of the type of treatment indicated from that appraisal would seem to be a more logical approach. Too little is known about asphyxia to warrant complacent acceptance of any one method of treatment as the final answer. The stimulus for further search for the causes and for other methods of treatment would be dulled by such a course. Acceptance of a machine as a replacement for personal responsibility in medical practice is dangerous, not only from the standpoint of the patient's welfare but from the standpoint of medical practice as well.

*Hormonal Influences.*—The various effects of prenatal and postnatal hormonal factors on neonatal physiology are becoming more widely recognized. Disturbances due to severe maternal endocrine imbalance such as exists in diabetes and in thyroid dysfunction are quite clearly understood. Also the occurrence of the so-called pregnancy reactions (breast engorgement, lactation, vaginal bleeding, and the like) is common knowledge. In tetany of the newborn infant transient hypoparathyroidism resulting from the physio-

logic maternal hyperparathyroidism of pregnancy is quite generally accepted as one etiological factor. Other factors concerned in producing the clinical picture of hypocalcemic tetany are: low capacity of the kidneys to excrete phosphates, and the low calcium-phosphorus ratio in the usual cow's milk formulas fed to newborn infants.[67] Accurate diagnosis of this condition remains difficult. Dodd and Rappaport[68] recently studied a comparatively large series of cases and many of their findings are enlightening from the standpoint of symptomatology and diagnosis. In addition to varying degrees of neuromuscular irritability, vomiting was a common symptom, and edema was quite often a prominent finding. In a group of twenty-four infants with symptoms of tetany the serum calcium levels were 6 to 9 mg. per cent and about one-third of these patients had serum phosphorus levels above 8 mg. per cent. In forty-eight infants without symptoms of tetany only five had serum calcium levels below 9 mg. per cent and only two had serum phosphorus levels above 8 mg. per cent. Since the symptoms are those which are often seen in other pathologic conditions, and since low calcium and high phosphorus levels are not always associated with symptoms of tetany, care should be exercised in ruling out organic pathology of the central nervous system before making a diagnosis of tetany. There can, however, be no doubt of a significant relationship of clinical symptoms to low serum calcium and high serum phosphorus levels. Prompt and dramatic disappearance of symptoms following the administration of calcium makes the diagnosis a fairly justifiable assumption.

The great interest in hormones of the adrenal cortex and the unique anatomic peculiarities of this structure in the newborn infant, its relatively large size at birth and rapid hypoplasia or regression during the neonatal period, have given rise to considerable speculation regarding its role in the physiologic picture of neonatal adjustments. Jaudon[69, 70] has described a clinical syndrome which he considers due to temporary adrenocortical insufficiency in the neonatal and early infancy period. It is characterized by vomiting, failure to gain weight, and periods of unexplained dehydration accompanied by low serum chloride levels, low sodium and often elevated postassium levels, resulting from excessive renal excretion of sodium, chlorides, and water. The condition is corrected by the administration of desoxycorticosterone acetate, and increasing the intake of sodium chloride. In a matter of a few weeks treatment can as a rule be gradually omitted without the return of symptoms. There has not been general acceptance of this clinical picture as an entity. It is certainly not a common one in the experience of most pediatricians. But it surely merits further study since hormonal imbalance involving the hormones of the adrenal cortex could very logically be expected to occur in the newborn infant.

A recent paper by Knudson[71] calls attention to the fact that when adrenal insufficiency is suspected it may be due to mixed adrenal disease. This disease is not transient; there is good evidence that it is based on a genetic trait. Persistent forceful or projectile vomiting is an early symptom and is associated with rapid dehydration and loss of weight, and in some instances circula-

tory collapse and cyanosis. In females there is usually pseudohermaphroditism, while in males evidences of virilism are not likely to be present in the newborn period. In addition to excessive loss of chlorides by the renal route there is also excessive excretion of 17-ketosteroids in the urine. In temporary adrenal insufficiency of the type described by Jaudon, urinary excretion of 17-ketosteroids is normal. Because projectile vomiting is an early and prominent symptom in mixed adrenal disease a diagnosis of pyloric stenosis has been erroneously made in several recorded cases. This error can be avoided through laboratory studies. In pyloric stenosis there is metabolic alkalosis due to loss of chlorides by vomiting of gastric secretions and urinary chloride excretion is decreased. In adrenal insufficiency there is increased urinary chloride excretion, the serum bicarbonate value is low and there is metabolic acidosis, and excessive excretion of 17-ketosteroids is diagnostic.

In summary it can be said that the response of the fetus to the maternal endocrine peculiarities of pregnancy and the changes occurring in its own endocrine glands under the influences of intrauterine environment is reflected in many anatomic and physiologic peculiarities in the period of adjustment after birth. For the most part these are transient and harmless, but under some circumstances may give rise to serious symptoms. It is quite probable that an increasing number of neonatal characteristics will be found to have their basis in such hormonal factors. Recently, for example, Smith[9] suggested that in physiologic edema there might well be an endocrine factor in its etiology.

*Renal Function.*—There is a lower functional capacity of the kidneys of newborn infants in terms of comparison with the kidney function of older infants and adults. Immaturity of the kidneys is probably responsible. It is more pronounced in infants born prematurely than in those born at term.[7-11] The practical importance of this knowledge is that the newborn infant, especially the premature, is in a more or less precarious state of delicate electrolyte and water balance; he is even in a state of mild acidosis when receiving the usual artificial feeding formulas. His metabolic peculiarities are such that under normal conditions he suffers no harm, but conditions that put too great demand on renal function can produce untoward symptoms. It calls attention to the necessity for care in the selection of feedings and fluids, including parenteral fluids, when these are indicated. It has a bearing also on the dosage of drugs that are eliminated by way of the kidneys. Richmond and associates[12] demonstrated that blood levels of sulfonamides are obtained in the early weeks of life with a much smaller dosage of these drugs than is required for similar levels in older children.

*Neonatal Infections.*—There has been renewed interest in this subject, stimulated by: (1) availability of effective therapeutic drugs; (2) recognition of the poor immunologic response of the newborn infant to bacterial invasion; (3) growing appreciation of the role of viruses as etiological pathogens in neonatal infections; and (4) the crowded conditions and scarcity of adequate nursing personnel in maternity nurseries. In regard to sepsis of the newborn infant we are confronted by a peculiar situation. We

now have effective drugs for therapy but there remains the problem of early recognition of the disease. Sepsis has become so much less common through almost universal improvements in aseptic techniques that many of the present generation of actively practicing physicians fail to recognize the obscure early symptoms of the disease. More attention should be given to this subject in the training of physicians because, in spite of good technique in newborn care, sepsis is still with us.

Epidemic diarrhea of the newborn has not been so prevalent in recent years. Scattered epidemics of diarrhea have been reported, some caused by demonstrated bacterial infections due to breaks in aseptic technique, and others of unexplained origin. Whether or not all of these should be classified as epidemic diarrhea of the newborn is open to argument; some say not. The question is rather academic since, no matter what the etiological agent or agents may be, each epidemic should be subjected to the same kind of searching investigative and control measures. Virus etiology, while strongly suspected in many epidemics, has been proved in few. It still remains, however, in the forefront of suspicion. In the realm of treatment the outstanding work of Darrow and associates[73, 74] has pointed the way toward intelligent management of these patients.

*Intracranial Birth Injury.*—This subject has not been blessed by any startling revelations that can assuredly promise lowered incidence of, or more effective treatment for, intracranial birth injuries. A possible exception to this statement is in those injuries resulting in subdural hematomas. While clinical symptoms of this condition do not usually become evident in the neonatal period, it is quite certain that birth injury is a common cause. The present widespread interest in this subject will undoubtedly result in an increasing number of cases being recognized at an earlier period after birth than has been the case in the past. The well-developed clinical picture has been clearly described and is quite generally recognized, as is also the method of treatment.

The value of repeated spinal taps in the treatment of intracranial hemorrhage is still controversial. Temporary relief of symptoms can unquestionably be obtained in some instances, but whether or not the ultimate status of the infant is improved is an open question.

The electroencephalographic studies of Hughes and co-workers[75] have given some much needed information on the brain wave patterns of newborn infants and some hope that early evidence of brain damage may be derived from such tests. It is still too early to say how reliable this information will be for diagnostic purposes.

### III. SURGERY OF THE NEWBORN INFANT

One of the most important and certainly the most spectacular of the recent advances in the care of the newborn infant has been in the field of surgery. Conditions that only a few years ago were hopeless are now successfully treated by astounding surgical skill and ingenuity. These advances have been made possible through improvements in many fields; in anesthesiology, in techniques of parenteral feeding and fluid and electrolyte control, and in control of infections. Probably the greatest advances have been in thoracic surgery. This has made possible the surgical

correction of congenital anomalies of the esophagus, trachea, lung, and of the heart and great vessels. This progress has given stimulus to intensive study of pathologic conditions of thoracic organs and of diagnostic methods which have produced refinements in precision of differentiation of types of lesions. Mention need be made only of the contributions of the roentgenologists, the cardiologists, and the pediatricians as well as the surgeons to emphasize that progress has been the result of group effort.

Significant advances have been made in improving the plight of newborn infants with various types of intestinal obstruction. This has been not only from the standpoint of surgical and medical management, but from the very important standpoint of early diagnosis as well. Wasch and Marck[76] made one of the most valuable contributions to early diagnosis in their study of the normal pattern of air-filling of the intestinal tract in the first day of life. They made systematic roentgenographic studies of fifty normal newborn infants at frequent intervals from birth throughout the first twenty-four hours and found that the sequence of filling of the various divisions of the gastrointestinal tract follows a quite well-defined pattern and that the time table of the passage of air is a fairly constant one. This is a summary of their findings: (1) air is present in the stomach promptly after birth; (2) within the first hour the proximal portion of the small bowel is outlined, mostly in the left upper abdomen; (3) between the first and third hours the remainder of the small bowel fills and segments of the large bowel first appear, the ascending and the descending colon and in some cases even the distal portions of the colon by three hours; (4) from the fourth to the eighth hour there is a progressive increase in the amount of air distributed in both small and large bowel; (5) at the eighth hour the striking finding is the presence of innumerable air-containing segments of small bowel closely packed and filling the abdominal cavity, in contrast to the relatively lesser amount in the colon; (6) following the first feeding (which in the case of these infants was at eight hours) the relative proportion of air in the small bowel as compared to the large bowel changes in favor of the latter. Segments of air-filled small bowel become fewer, poorly defined, and widely separated, while the limbs of the colon become more prominent; (7) at the twelfth hour this distribution becomes established and continues as the characteristic pattern to the end of the infant's first day. More universal application of this knowledge should greatly decrease the necessity for the use of contrast media in the roentgenologic examination of newborn infants suspected of having intestinal obstruction. It is considered safer for the infant.

Weiner and Richmond[77] emphasize the importance of early diagnosis of conditions of the newborn infant that may be corrected by surgery in the statement that, in 1947, congenital anomalies caused 4.6 deaths out of each 1,000 live births, a figure second only to prematurity as a cause of death in the neonatal period.

### IV. PREMATURE INFANTS

The great amount of attention paid to premature infants in recent years was logically to be expected. Approximately 50 per cent of all neonatal deaths occur in this group although they make up only 6 per cent of the

total number of live births in the country as a whole. Space will permit only a summary of what seems to be the most important findings from a practical standpoint.

"Premature" is the term almost universally applied to all infants born alive weighing 2,500 grams or less. This includes a group with many dissimilarities and to appraise the status of individual members of this group it is essential to recognize these modifying factors. Simply using the term "premature" is not enough. The infant weighing 1,000 grams at birth has little resemblance to one with a birth weight of 2,500 grams.

Birth weight has a significant relationship to gestational age and, for that reason, to the probabilities of survival. It is about the only practical measure we have for obtaining information that is relatively reliable for statistical comparison on a national and international level. Steiner and Pomerance[78] have recently called attention to the influence of maturity upon survival rates in each of the birth weight categories of premature infants and emphasize the inaccuracies of birth weight as an index to gestational age. But we have as yet no really accurate and practical measure of gestational age, and, until we have, birth weight must continue to be the statistical yardstick. Such studies are nevertheless important because they emphasize the necessity for careful individual evaluation of premature births in clinical practice. Some of the things that need to be kept in mind in such an evaluation are: (1) sex—more females fall in the premature weight group than males; (2) race—nonwhites have a lower mean birth weight than whites; (3) variations in rate of maturation—in general females mature more rapidly than males, and Negro infants than white infants (Christy's[79] studies on appearance of centers of ossification); (4) variations in inherent growth potentials—some infants with birth weights as low as 2,000 grams or even less are simply small because of parental stock and not because of premature birth; (5) single or multiple births—twin pregnancies tend strongly to premature labor, but it is also true that twins carried to term have a lower mean birth weight than single term infants; (6) geography—altitude appears to have an influence on birth weight.[80] Mean birth weight is lower in regions of high altitude than in regions of low altitude; (7) the prenatal history—maternal health and nutrition have an effect upon fetal growth as do also local intrauterine conditions and factors that determine the size and efficiency of the placenta; and (8) anatomic and physiologic evidences of prematurity—here the experience, knowledge, and acuity of observation of the clinician must be depended upon. It is obvious that an accurate assessment is possible only through free collaboration of obstetrician and pediatrician.

The functional capacity of organs and tissues is dependent upon gestational age or the stage of maturity reached at the time of birth. Studies on premature infants have illustrated this in a clear manner. Restricted functional performance of the kidneys,[7-11] of the liver,[12, 13] of the respiratory mechanism,[2, 4, 81] of the mechanism for acid-base control,[9, 82] and of the digestive system[83] has been shown to depend upon, and to constitute an index of maturation. All of these are important additions to our knowledge

and help in forming the basis for intelligent management of the premature and also of the full-term infant.

Contemplating these inefficiencies of physiologic performance might well excite awe and wonder that so many, even among the very immature, survive rather than that the fatality rate is high. Viewing them in terms of what is considered normal for older infants is a distortion of the picture. It is necessary that the metabolic processes at that stage of maturation be taken into consideration to make the picture clear. Reardon and co-workers[82] reported a wide range in the chemical findings among normal premature infants. Sixty-seven per cent had findings of an uncompensated metabolic acidosis but there was no correlation between variations in the acid-base disturbance and the prognosis for life. But according to these investigators the fact that most premature infants do have an unstable acid-base balance may be a reason why they so easily develop severe acidosis when any stress occurs. Their conclusion is that the cause of acidosis in premature infants has not been established. The theory that they have a partial anaerobic metabolism is tenable but not yet proved.

One thing is clear, that in spite of the many apparent faults and deficiencies of the premature infant, these are not necessarily unsurmountable handicaps, and more harm than good may often result from efforts to "correct" them. But, at the same time, these deficiencies must be taken into consideration in the care of the premature infant so that stress, which may readily disturb their equilibrium, can be avoided in so far as possible.

Feeding of premature infants has undergone no marked changes in the last few years. Knowledge of food and fluid requirements is quite generally understood and applied. The studies of Madey and Dancis[84] and of Feinstein and Smith[85] indicate that there is no significant impairment of protein digestion due to prematurity and that protein hydrolysates have no superiority over whole casein in the feeding of premature infants.

It is well established that absorption of fats is poor. Fat-soluble vitamins in a water-miscible dispersion are, however, readily absorbed. Morales and associates[83] have recently stressed the advantages and the desirability of fats in nutrition and have shown that by reducing particle size through a process of homogenization much better absorption of dietary fat was obtained than with unemulsified fat. They suggest that more refined procedures should be capable of still greater reduction of particle size and even better absorption. Just as improvements in absorption of fat-soluble vitamins were obtained with a fine aqueous dispersion, similar improvements may be expected with dietary fats in the future.

The studies of Glaser and associates[86] proved quite conclusively that the dosage of vitamin D need not be greater than 400 units per day to protect the average premature infant from rickets and that a dosage between 400 and 800 units per day was adequate and safe.

Less concern about meeting fluid requirements in the early postnatal days and a longer thirst and hunger period is in vogue in several premature centers. It is still too early to say whether this practice is wholly good or whether some of its advantages

may be offset by other effects that are harmful. More individualization rather than blanket orders would seem preferable. This subject needs further clinical evaluation.

Experiments with the administration of testosterone propionate and methyl testosterone as an aid to nitrogen retention have not demonstrated satisfactory evidence of beneficial effects.[87]

The use of an indwelling polyethylene nasal catheter for the feeding of the more premature group of infants has been suggested by Royce and coworkers.[88] This is deserving of serious consideration. It obviates the necessity for frequent passing of a gavage tube with its inherent dangers especially when adequately trained nursing personnel is not available around the clock.

The chief threats to life continue to be respiratory difficulties, infection, and intracranial hemorrhage. The problem of hyaline membrane looms large and has yet to be solved. There is reason to believe that more attention to humidification of inspired atmospheric air and oxygen mixtures may have prophylactic value.

The "Isolet" is proving a helpful adjunct in the prevention of infection but does not remove the necessity for strict aseptic technique and well-trained nursing personnel to accomplish this purpose.

An interesting commentary on the care of premature infants has come from Newcastle upon Tyne, England. A comparative study of home versus hospital care was made. Home care was under the supervision and with the aid of visiting nurses. The study showed that for infants weighing less than 3½ pounds at birth, hospital care was superior, there being a significantly lower fatality rate, but infants with birth weights above 3½ pounds did equally well at home as in hospitals.[89]

Retrolental fibroplasia has occupied a conspicuous position in pediatric and ophthalmologic literature during the past ten years. All pediatricians are acutely aware of this serious disease and there is no need of a detailed review here. It appears to be caused by some factor or factors rather recently introduced into the environment of the premature infant or that of its mother, or both. The offending factor or factors have not yet been discovered. The disease occurs almost exclusively in the more immature of the prematurely born infants, those with birth weights of 1,500 grams or less. The incidence varies greatly in different centers for the care of premature infants. The different methods of care in hospitals having a high incidence and those with a low incidence have been compared item by item, but as yet no significant clue has led to a satisfactory answer. Many suspected factors have been studied and others are now under investigation. As yet no method of treatment has been effective.

### V. ROOMING-IN

This method of caring for the newborn infant seems to be gaining approval in hospitals in many parts of the country and probably will be more and more widely practiced at least on an elective basis. Some of the factors responsible for revival of this system are: (1) realization of the hazards of infection in large maternity nurseries; (2) shortage of nursing personnel; (3) growing interest in the emotional and psychologic aspect of

parent-infant relationship; (4) a belief that closer physical association of mother and infant will promote breast feeding; and (5) the advantage of giving the mother firsthand acquaintance with her infant and personal experience in caring for him under supervision before taking him home. Whether or not the hoped-for results will be forthcoming cannot yet be predicted with certainty. It has not been in operation long enough nor on a wide enough scale for accurate evaluation. Reports from some sources have been most enthusiastic while from others enthusiasm has been qualified. Not all obstetricians and pediatricians have looked upon it with favor, but this may well be because they have not seen it in operation under the best of circumstances. In most hospitals where it is in operation it is on an experimental and elective basis, a general maternity nursery being maintained as usual in addition. McBryde's[90] report from Duke University Hospital where rooming-in is compulsory for all patients is more convincing than any reports thus far published. He contends that by using this system exclusively costs of nursing care can be materially reduced. This would be an advantage of considerable importance. No substantiation of this has yet come from other sources, to my knowledge.

We can do little at present but speculate on the possible and probable effects of rooming-in. (1) Will neonatal infections be decreased? At least the number of sources of contact infections and of air-borne infections will be fewer, but the danger from ingested pathogens will be essentially unchanged. Necessity for strict adherence to rules of aseptic technique will remain. (2) Reduction in nursing costs can reasonably be expected in hospitals where rooming-in is universally applied. (3) Promotion of breast feeding should be expected from the close association of mother and infant. With the mother participating in her infant's care and in constant proximity to it, a good setting for breast feeding exists, and the mechanical difficulties inherent in nurseries with their dependence upon rigid routine will be eliminated. All this will be advantageous to the mother who wishes to nurse her baby and will increase the possibilities of her being able to do so. This advantage will, however, be largely dissipated unless a marked change occurs in the present widespread indifference and, in some instances, even opposition to breast feeding on the part of physicians and nurses. There is encouraging evidence that a change in attitude is taking place and there is hope that in a few years a survey will show a definite change in favor of breast feeding when compared to the figures from the survey recently made by Bain.[91] (4) Of especial importance is the opportunity afforded the mother to know her infant and learn under supervision the practical points of its care. There is an opportunity here for alert, intelligent, and well-informed nurses under adequate medical guidance to teach the mother much that will help to make her subsequent care of her infant interesting and less harassing. (5) The psychological and emotional advantages claimed to accrue from rooming-in are difficult to evaluate. One obvious and important advantage is satisfaction of the mother's sense of possession that can come from having her baby constantly with her, and

realization from the first rather than later that responsibility for its comfort and happiness is hers now and always. What other psychologic, emotional, and spiritual values may come from rooming-in no one can say. The answer can certainly not be given by physicians or nurses, not even by psychiatrists. Perhaps some of its good influences will be reflected in the behavior of future generations.

It is realized that the contributions of many investigators and authors have been omitted in this review and that the contributions of many others have been given scant mention. For those who wish comprehensive discussions of the subjects reviewed references may be found in the attached bibliography.

All whose interests have been in this field of pediatrics are gratified by the increasing attention being given to the newborn infant. It is a hopeful sign of a brighter outlook in "The Valley of the Shadow of Birth."[92]

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# Psychologic Aspects of Pediatrics

## THE PSYCHOLOGIC EVALUATION OF CHILDREN WITH CEREBRAL PALSY AND ITS IMPLICATIONS IN TREATMENT

PRELIMINARY REPORT

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IT HAS been apparent that many of the children referred to the Cerebral Palsy Center of the Buffalo Children's Hospital for treatment are handicapped mentally as well as physically which creates a serious problem in treatment and schooling and severe emotional strain on the family.

In the study of these patients at the Psychosomatic Clinic the psychologic evaluation plays an important role in understanding and treating the child. One of the first questions to be answered is whether the child is treatable, and an important factor is his mental capacity. This is important not only in trying to determine the possibilities of working with the child, but in trying to plan treatment. If the child can not be helped physically, there is still an obligation to the child and his family to help them plan toward the future. If he can be helped there is an obligation to initiate the most effective and economical way of doing so.

In order to better understand the extent of the psychologic handicap we have thoroughly studied the records of 330 children with cerebral palsy seen over a five-year period.

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This study is supported by the New York State Association for Crippled Children, Inc.

### MATERIAL AND METHODS

Every child who was studied in the Cerebral Palsy Diagnostic Clinic in the five-year period from Jan. 1, 1947, through Dec. 31, 1951, and diagnosed as having cerebral palsy is included in this group. There were 300 new patients during this period. The other thirty were children who had had their initial contact some time prior to 1947, but were still under treatment during this five-year period.

The patients' records include the physical examination consisting of pediatric, orthopedic, and neurological examinations, reports of x-rays and electroencephalograms, and any special examinations indicated in individual cases. Detailed reports of every psychologic examination given and of the social history are included. The medical diagnosis accepted for this report was the one agreed on at the conclusion of the study of each child, when all findings were pooled and discussed in conference.

It should be noted that a large number of children studied in the Cerebral Palsy Diagnostic Clinic during this five-year period were not diagnosed as cerebral palsy. In the large majority of such cases, the diagnosis was mental deficiency with associated retarded physical development. Such children are not included in this study.

*Evaluation of the Severely Handicapped.*—The psychologic examinations used for purposes of obtaining an intelligence rating were the Stanford-Binet, Form L, and the Cattell Infant Intelligence Scale. Of the 330 children, 263 or 80 per cent were evaluated by one of the above intelligence scales. Not all of these 263 children, however, and particularly the severely handicapped, could be evaluated by the psychologic examination in its standard form.

To overcome the problems of lack of good speech and co-ordination, testing techniques were modified when necessary to suit the individual child. We have found this a useful and practical way of meeting the needs of these children with multiple handicaps.

Departure from standardized procedure has not been established as valid. The criteria of validity of modifying the standardized tests have been the clinical criteria based upon observations of these children and their reactions and progress over a period of many years. The ratings obtained fit so closely with our prolonged observations of these children that we feel that they would deviate very little from ratings obtained if a standardized procedure were possible. They are not presented, therefore, as estimated values. Any deviation would be small and likely to be in the direction of overrating since modifications tend to simplify the tests somewhat. Any method of response the child could use was accepted, even if it consisted only of moving his eyes, shaking his head, or pointing or pushing. Multiple choice was substituted for material requiring verbal discriminations when speech was lacking; enlarged objects were more stimulating for many children than the same objects in miniature as on the standardized test; even recognition of numbers, knowledge of number concepts, recognition of words and letters, could all be ascertained in the nonverbal and severely handicapped child by capitalizing on his way of responding, no matter how crude it might be. Many areas of ability could be tested by using the actual content of the standardized test, but altering its administration and prorating results. A great many of the children could be given standardized tests with little or no modification.

Twenty per cent of the children were unable to respond to any testing procedure, no matter how it was modified. All disabilities, whether in coordination, speech, vision, or hearing, were considered in every evaluation, but when there was such a combination of disabilities, or such a lack of awareness or comprehension that no testing was possible, the child was subjectively evaluated. In making subjective evaluations many bits of evidence and clinical judgment are used. Reactions to surroundings, parents' reports as to reactions at home, and attempting to glean from their reports those things which are meaningful developmentally are important parts of the evaluation. It is sometimes possible to select one or two items the child can respond to from one developmental scale, and two or three from another, and get some factual though spotty evidence that he can function to some extent at certain developmental levels. The comparison of one child with a simi-

larly or even more severely handicapped child is one of the very useful procedures with the "untestables." He may still be capable of responding and give many indications of understanding language, for example, even if he can not speak. He may show evidence of wanting to play even if he can not manipulate well enough to carry out his ideas. There is a distinct difference between the severely handicapped but eager and interested child with cerebral palsy and the severely handicapped but entirely disinterested, unresponsive child who gives no indication of much comprehension of what is going on about him. Many of the subjectively evaluated children had only a moderate or slight physical handicap, but that slight handicap, in combination with apparently a very severe mental handicap, is enough to make the child incapable of responding to an actual test situation. It is of fundamental importance that the psychologist making such evaluations be an experienced clinical psychologist and also have specialized experience with children with cerebral palsy. It is always possible for a diagnosis to be incorrect on both the untestable and testable children, and certainly there will be errors in this field as in any other. We believe such errors have been at a minimum in this study.

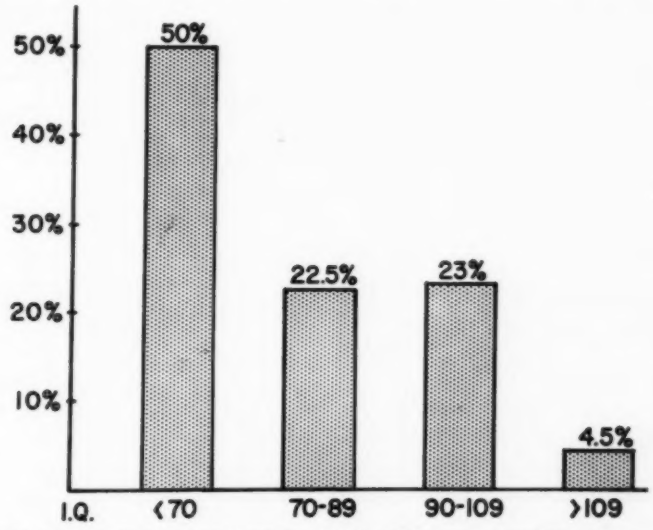


Fig. 1.—Intelligence classification of 330 children with cerebral palsy.

TABLE I. INTELLIGENCE DISTRIBUTION OF 330 CHILDREN WITH CEREBRAL PALSY

| I.Q. | | NUMBER | PER CENT | |
|---|---|---|---|---|
| <70 | 40 | 74 | 22.5 | 50 |
| | 40- 59 | 51 | 15.5 | |
| | 60- 69 | 39 | 12.0 | |
| 70-89 | 70- 79 | 38 | 11.5 | 22.5 |
| | 80- 89 | 36 | 11.0 | |
| >90 | 90-109 | 77 | 23.0 | 27.5 |
| | 110+ | 15 | 4.5 | |

## RESULTS

A breakdown of the 330 cerebral palsy children into intelligence levels

shows (Fig. 1; Table I) that one-half of the children are mentally deficient (below 70 I.Q.) and about three-fourths (72.5 per cent) are of below average ability (below 90 I.Q.). Only about one-fourth are average or above (above 90 I.Q.).

The breakdown of the intelligence classification according to cerebral palsy type is shown in Table II. There is no appreciable difference in intelligence between the athetoids and spastics. The other groups are too small for the figures to be meaningful.

TABLE II. INTELLIGENCE DISTRIBUTION WITHIN THE CEREBRAL PALSY TYPES

| | SPASTIC (209) | | ATHETOID (83) | | ATAXIC (27) | | MIXED (11) | | TOTAL (330) | |
|---|---|---|---|---|---|---|---|---|---|---|
| I.Q. | NO. | % | NO. | % | NO. | % | NO. | % | NO. | % |
| Below 70 | 106 | 51 | 43 | 52 | 9 | 33 | 6 | 55 | 164 | 50 |
| 70- 89 | 39 | 19 | 25 | 30 | 8 | 30 | 2 | 18 | 74 | 22.5 |
| 90-109 | 54 | 25 | 13 | 16 | 7 | 26 | 3 | 27 | 77 | 23 |
| 110+ | 10 | 5 | 2 | 2 | 3 | 11 | 0 | 0 | 15 | 4.5 |

The intelligence distribution of our 330 children with cerebral palsy is compared with that of the normal population in Fig. 2.

The findings recently reported by Asher and Schonell[1] in England in a study of the intelligence distribution of 354 children with cerebral palsy are shown in Fig. 3. The marked similarity between the results of the two studies is striking.

Since our findings are in contrast to statements that have been made in the past,[2, 3, 4, 5] two factors which might tend to boost the number we have classified as mentally defective have been studied.

1. *Possible Selectivity of Patients.*—A factor possibly operating selectively to increase the percentage of mentally defective children in this study is the large number of children seen from other areas in the state or neighboring states who might have been brought to this clinic as a "last resort." Such children might have been considered unable to profit from treatment. In order to investigate this possibility, all the children who were not from Buffalo or the nearby suburban areas and small towns were studied separately and compared with the whole group. Table III shows that there were no important differences in intelligence in the "out-of-town" group and the total group. This was not a selective factor, then, in our series.

TABLE III. EFFECT OF "OUT-OF-TOWN" CEREBRAL PALSY PATIENTS ON INTELLIGENCE DISTRIBUTION

| I.Q. | "OUT-OF-TOWN" GROUP (125) (%) | TOTAL GROUP (330) (%) |
|---|---|---|
| <70 | 49.0 | 50.0 |
| 70-89 | 25.5 | 22.5 |
| >90 | 25.5 | 27.5 |

2. *Effect of Subjective Evaluations on the Intelligence Distribution of the Total Group.*—Out of the entire group of 330 children, sixty-seven (20 per cent) were subjectively evaluated. In Table IV, these were ex-

TABLE IV. EFFECT OF SUBJECTIVE EVALUATIONS ON INTELLIGENCE DISTRIBUTION

| I.Q. | OBJECTIVE GROUP (263) (%) | TOTAL GROUP (330) (%) |
|---|---|---|
| <70 | 44.0 | 50.0 |
| 70-89 | 24.0 | 22.5 |
| >90 | 32.0 | 27.5 |

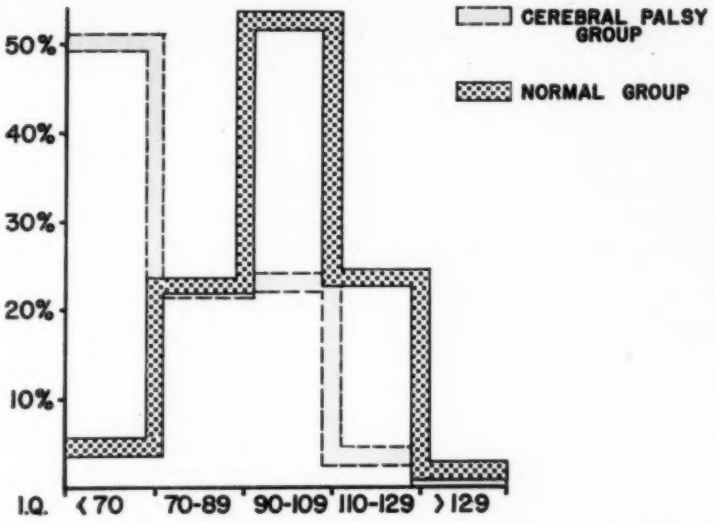


Fig. 2.—Distribution of I.Q. of cerebral palsy group versus normal group.

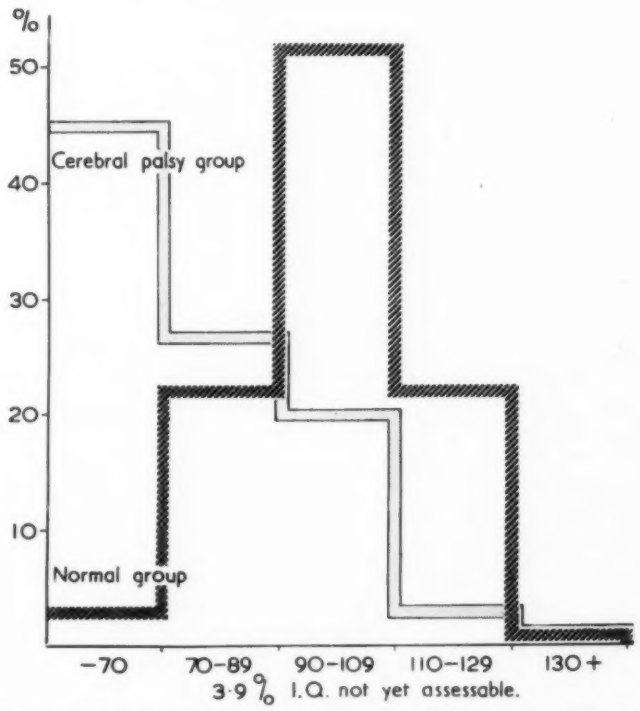


Fig. 3.—Distribution of 354 estimated I.Q.'s of cerebral palsy group compared with distribution of those of normal child population as found in England. (From Asher and Schonell: Arch. Dis. Childhood 25: 360, 1950.)

cluded and the intelligence distribution of the other 263 children is compared with that of the total group. The incidence of mental deficiency continues to be extremely high. The inclusion of subjective evaluations does not markedly affect the intelligence distribution. Of the sixty-seven children subjectively evaluated, fifty-one were rated as mentally defective. Thirty-four of these were re-evaluated over a period of one to ten years. There were from one to five re-evaluations per patient. During this interval, eleven of the children became capable of responding to standardized tests. The test findings confirmed the earlier observation of mental deficiency. On re-evaluation, twenty-six patients were given a somewhat lower rating, eight were given the same rating, and none were rated higher. A lower rating on re-evaluation indicates that there is a tendency to rate the child as high as possible when he is first evaluated, and does not imply that the child is deteriorating mentally.

## DISCUSSION

The data presented show that the intelligence distribution of cerebral palsy children deviates markedly from the normal. One-half of the children are mentally defective—three-fourths are below average in intelligence. The implications of these findings are of great importance. They do not imply that only one-fourth of these children can be treated, but that there is a need to revise planning for treatment and schooling, and to provide more facilities for those children who cannot benefit from either. More teachers must be trained for defective and dull cerebral palsy children than for average cerebral palsy children. There are many children who can profit from physical therapy but may not be mentally capable of deriving any benefit from occupational or speech therapy, or from much schooling.

Oftentimes the child is given a trial of treatment in all areas for a period of three to six months in order to evaluate treatability. A child who has the capacity to actively take part in a physical therapy program but not in other areas of treatment may become so frustrated by his failures in the latter that his progress in physical therapy would be impeded. A true trial of treatment should be selective rather than general.

A number of the low grade defective children (22.5 per cent below I.Q. of 40) do not have the intellectual capacity to take part in even a limited training program. Including such children in a treatment program is not indicated. The parents are subjected to false hopes and a prolonged period of uncertainty. Most of these children will eventually need institutionalization.

In order to use time, money, and trained personnel to the best advantage, the program must be related to (1) the child's ultimate capacity, and (2) his mental level at the time he is being considered for treatment.

1. *The Child's Ultimate Capacity:* Twenty-seven and five-tenths per cent of the children are in the middle and high grade defective group. Many of these children are not educable to any great extent academically. Some of them, however, particularly the less severely handicapped, will be trainable physically to help them become more self-sufficient. It is as im-

portant for these children as for any other child to learn to walk. However, some of these children will be mentally unable to perfect or even greatly improve their hand coordination or articulate more clearly. A treatment program concentrated on walking and self-care with the recognition that other skills may never be developed would be indicated for many in this group. The long range aims of treatment will be fulfilled more frequently in a program related to the child's ultimate capacity.

2. *The mental level of the child at the time he is being considered for treatment:* The immediate aims of treatment should be related to both the mental and chronologic age. Table V gives the age distribution.

TABLE V. AGE DISTRIBUTION OF 330 CHILDREN WITH CEREBRAL PALSY WHEN FIRST SEEN

| AGE (YR.) | NUMBER | PER CENT |
|---|---|---|
| 0- 2 | 42 | 13 |
| 2- 4 | 143 | 43 |
| 4- 6 | 59 | 18 |
| 6- 9 | 32 | 10 |
| 9-12 | 34 | 10 |
| 12+ | 20 | 6 |

Fifty-six per cent of the 330 children with cerebral palsy were under 4 years of age. Fifty-three per cent of these were mentally defective (I.Q. under 70). Within this defective group, 61 per cent had an I.Q. under 40.

TABLE VI. INTELLIGENCE DISTRIBUTION OF CHILDREN UNDER 4 YEARS OF AGE (185—42 UNDER 2 YEARS; 143 FROM 2 TO 4 YEARS)

| I.Q. | NUMBER | PER CENT |
|---|---|---|
| Below 40 | 60 | 32.5 |
| 40- 59 | 25 | 13.5 |
| 60- 69 | 13 | 7.0 |
| 70- 79 | 15 | 8.0 |
| 80- 89 | 15 | 8.0 |
| 90-109 | 48 | 26.0 |
| 110+ | 9 | 5.0 |

A large number of these children below 4 years of age have not as yet attained a mental age where they are ready for some types of treatment or possibly for any treatment. Developmentally they have not as yet reached a point where they are able to understand and take part in treatment. A large percentage of them are below 2 years mentally and some below 1 year at the time of acceptance for study.

The chronologic age must be considered as well as the mental age. A 3-year-old child with a mental age of 18 months is not the alert, responsive, and fast learning child that the normal 18-month-old baby is. His problems of comprehension, concentration, and motivation, his slow learning rate, and his social immaturity are all handicaps. Though he has a mental age of 18 months, he is not a normal 18-month-old baby, but a mentally defective 3-year-old.

The immediate aims of treatment for such a child would have to be extremely limited or treatment might have to be postponed. This also applies to other age groups and various levels of ability. Since present tendency is to refer children when they are quite young, it has become very important to consider their readiness for treatment. Such thinking is not designed to eliminate more children from treatment—it is a way of more effectively meeting the needs of more children with available facilities and personnel.

*Distractibility and Visuomotor Disturbances.*—During the psychologic examinations, many specific problems of the child are revealed, both through actual tests and the observations that can be made. Frequently emotional

reactions of various types are found as well as specific abilities and disabilities that are important in the total adjustment of the child. Any such findings are important to every person working directly with the child or with his parents. Two specific disabilities, distractibility and visuomotor disturbances, affecting both treatment and schooling were studied. Table VII reveals the frequency with which we find distractibility and visuomotor disturbances in the spastic and athetoid children over 4 years of age. Other types of cerebral palsy have been eliminated because of the small numbers of cases.

TABLE VII. DISTRACTIBILITY AND VISUOMOTOR DISTURBANCES IN 141 CHILDREN OVER 4 YEARS OF AGE WITH CEREBRAL PALSY

| | DISTRACTIBILITY | | VISUOMOTOR DISTURBANCE | | BOTH | |
|---|---|---|---|---|---|---|
| | NO. | % | NO. | % | NO. | % |
| Spastic (80) | 35 | 44 | 31 | 39 | 18 | 22.5 |
| Athetoid (52) | 21 | 40 | 4 | 8 | 2 | 4 |
| Ataxic (9) | 6 | -- | 5 | -- | 4 | -- |

By distractibility we mean the inability of the child to direct his attention to the central subject upon which he needs to concentrate in order to comprehend a situation. He is attracted by everything else around him instead—the focal point does not remain a focal point long enough for him to deal with the problem.

By visuomotor disturbances we mean the lack of ability to copy, match, remember, or visualize simple forms, and the distortion of such forms when the child tries to reproduce them, even though he has the necessary coordination and mental ability to enable him to do so.

Many of the children, particularly the very young ones, do not have the necessary coordination to engage in visuomotor activities. Because of this, and because distractibility cannot readily be detected in the very young child, we limited our study of these problems to the group over 4 years of age. Even in this group of 141 children not every child could be evaluated for these disabilities. The percentages based on the total group are, therefore, minimal.

When distractibility is present, the therapist and teacher have to contend with a child who cannot keep his mind on what he is trying to learn. Special techniques have to be set up to help him direct his attention. More frequent and shorter periods of therapy and schooling may have to be planned. The time necessary to achieve results may be appreciably lengthened.

If a child has a visuomotor disturbance his ability to learn by conventional methods of teaching is seriously impaired. The teacher and occupational therapist must devise new techniques. A child who has a visuomotor disturbance but is strongly attracted by color can be presented colored symbols in learning. These children can learn, but only if those working with them are aware of their problems and teach them accordingly.

We have not as yet studied many of the problems that come to our attention in working with these children, but we have begun to study a

few in which we have had an opportunity to gather factual data. There are many questions which need clarification. What, for example, is the level of mental ability necessary for a child to learn to walk if the handicap is not too severe? When is the child ready for various types of therapy? Are there some children who would profit more from one type of therapy at a time than from two or three types at a time? What should our aims of treatment and education be for each child, considering the combination of physical and mental potential? How do emotional disturbances in the children and their parents affect the progress of treatment? How can we apply ordinary developmental standards to treatment?

We are aware that the findings in this paper make the problem of the cerebral palsy child loom larger than ever. It is distressing that only one out of four children is an average child mentally. Surely the child with good intelligence should be given every advantage in schooling and treatment—he is our "best bet" in this group. But there are also the other three, and the problem of these will not be quite as tremendous if faced and dealt with realistically, for only then can we fit our program to the needs of each child and his family.

SUMMARY

The intelligence distribution of 330 children with cerebral palsy studied over a five-year period was obtained.

One-half of the children were mentally defective (I.Q. under 70) and three-fourths of them were below average intelligence (I.Q. below 90).

There is no relationship between type of cerebral palsy and intelligence distribution.

Of the 330 children, 56 per cent were under 4 years of age when first seen at the clinic. Of these, 53 per cent were mentally defective (I.Q. under 70), of whom 61 per cent were low grade defective (I.Q. below 40).

Two specific disabilities, distractibility and visuomotor disturbances, were studied. Forty-four per cent of the spastics and 40 per cent of the athetoids were very distractible. However, only 8 per cent of the athetoids, in contrast to 39 per cent of the spastics, showed visuomotor disturbances.

Implications of these findings are discussed. By fitting the treatment to the psychologic as well as the neuromuscular status of the individual child, aims of treatment would be more frequently fulfilled, and the tremendous parental emotional turmoil which unsuccessful and perhaps unindicated treatment engenders will be avoided.

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# Comments on Current Literature

## SURGICAL TREATMENT FOR MITRAL STENOSIS

ACCORDING to Wood[1] (1950) congenital heart lesions constitute only 2 per cent of all cases of heart disease, whereas rheumatic fever is responsible for 25 per cent of the cases of heart disease hospitalized, and in one-half of the latter, mitral stenosis is the predominate lesion. This grave type of cardiac involvement, and the serious crippling which results, prompted the British internist, Brunton, in 1902, to propose direct surgical reconstruction of the valve.[2]

> The good results that have been obtained by surgical treatment of wounds in the heart embolden one to hope that before very long similar good results may be obtained in cases of mitral stenosis.

Forty-six years later, in 1948, Brunton's suggested form of treatment became a surgical reality.[3] Judging from the large number of papers concerned with this operative procedure which has been published in the past four years, the results seem to be very encouraging. Two outstanding reports have appeared in recent literature: one from England in the *British Medical Journal* for May 17 (1952)[4] in which the authors present results in 100 patients with mitral stenosis who were treated by intracardiac surgery, and the other report in *Circulation* for September (1952),[5] in which a group of American physicians analyzes results obtained in 100 consecutive cases. Each group discusses in some detail the diagnosis, variations in surgical technique, the preoperative and postoperative care, et cetera. From the standpoint of the practicing physician, however, the most interesting phase of their work concerns the results which they obtained and the ultimate benefit to the patient.

The British workers report that in 100 patients who underwent mitral valvotomy, there were thirteen deaths. A detailed follow-up of the first fifty cases is summarized as follows:

| | |
|---|---|
| Deaths | 8 |
| Valvotomy not possible | 1 |
| Poor result | 5 |
| Fair result | 4 |
| Good result | 15 |
| Excellent result | 17 |

In discussing the thirty-two patients in whom the results were judged as "good" (fifteen) or "excellent" (seventeen), the authors evaluated the improvement in a very satisfactory manner by a comparison of the activity of the patient before the operative procedure with that following the operation. One patient, for example, "who could not walk the length of the ward before operation, when convalescing ran thirty yards for his last bus, missed it, and walked the necessary four miles without symptoms." In this group of thirty-two patients showing good or excellent results, two-thirds were able to resume work and could walk two miles or more.

The age at which operative intervention was undertaken in this series of patients is of considerable practical interest. Seventy-eight of the 100 patients were between the ages of 25 and 45 years; forty-seven of these were between 30 and 40 years of age. Only two patients were under 20 years of age (nineteen) at the time of surgery. The authors feel strongly that caution must be exercised in advising operative procedure prior to the age of 20 years, and express doubt that the operation should be undertaken at all in patients under the age of 17 years, because of the possibility that active rheumatic

carditis may interfere with the outcome. They hasten to add, however, that operative procedure may become imperative in the late teens, and that if the mitral stenosis is so severe as to threaten life, the age factor should not stand in the way. Improvements in technical surgical detail, and in preoperative and postoperative care of the patients have contributed their share in successful outcome. It is heartening to note that of the thirteen deaths occurring in the first 100 patients, seven were among the first twenty, and the remaining six fatalities were among the last eighty patients undergoing surgical procedure.

The American report comprises a careful analysis of 100 consecutive cases: patients with mitral stenosis who were treated by commissurotomy during the period March 22, 1948, to Nov. 14, 1950. In this series of patients the youngest was 17 years of age and the eldest, 53 years. In most instances the symptoms due to mitral stenosis prior to surgery were considered severe, and the lesion judged as far advanced. The authors used alteration of the patient's functional status as a means of evaluating the results of surgical procedure. The follow-up period in these patients ranged from one to three and one-half years. Thirty-two of the patients operated showed excellent results; forty-six were described as improved; nine showed little or no improvement. The surgical mortality in this group of 100 patients was considered to be about 11 per cent.

Again improvement in mortality figures was noted over a period of time: of five patients undergoing surgery in 1948, three died, a mortality of 60 per cent; among twenty-one patients in 1949, there were three deaths (14.2 per cent); among seventy-four patients operated upon in 1950 there were five deaths or a mortality of 6.7 per cent. An addendum at the end of this report carries the information that the series of patients has been extended as of May, 1952, a total of 274 patients with an operative mortality of 5.8 per cent. Marked and sustained improvement resulted in 76 per cent of the patients operated upon.

Such striking results obtained in the surgical treatment of mitral stenosis seem to fulfill in every respect the promise of the early reports and to justify surgical intervention. However, as is emphasized in these recent reports, patients who have suffered from mitral stenosis must be considered cardiac patients, regardless of the surgical results obtained, and still require the watchful care of their attending physicians.

RUSSELL J. BLATTNER

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# News and Notes

The Veterans Administration is instituting a four-month intensive training course in psychiatry and neurology to fit the needs of physicians without such previous training who are assigned to duty in twenty-two predominantly psychiatric hospitals. Physicians who have been engaged in general practice may request this training upon applying for a position at one of these hospitals.

The course will be held at the VA Hospitals in Coatesville, Pa.; Palo Alto, Calif.; and a joint Downey-Hines, Ill., program near Chicago, Ill. Physicians will be employed at salaries commensurate with their training and experience (salary range: $5,500 to $11,800 per annum) and assigned to the course with travel and per diem for the four-month period.

Information and applications may be obtained from your nearest VA Hospital or Regional Office, or by writing to the Chief Medical Director, Veterans Administration Central Office, Washington 25, D. C.

In October an in-patient psychiatric service for children was opened at the University of Minnesota Medical School and Hospitals. This new unit will materially strengthen the over-all child psychiatry program of teaching, research, and service which has been in operation since 1938. Expansion of the program was made possible by a legislative appropriation which also provided for increased staff and stipends for training in child psychiatry. A position as instructor is available for a qualified physician desiring an academic career. Those interested should contact Reynold A. Jensen, M.D., University of Minnesota Hospitals, Minneapolis, Minn.

# Book Reviews

**Infant and Maternal Care in New York City. A Study of Hospital Facilities.** E. H. L. Corwin, Director, New York, 1952, Columbia University Press, 188 pages. Price $3.50.

A report of a study of the hospital facilities in New York made under the sponsorship of the Committee on Public Relations of the New York Academy of Medicine. As 99 per cent of the births in New York are hospital deliveries, the study was limited to hospitals. The study gives a complete picture as 104 hospitals with maternity services were visited, and only three small proprietary hospitals declined to cooperate. Twelve of the 104 hospitals were municipal, sixty-two voluntary, and thirty proprietary institutions. The service in twenty-three was considered as "large" with fifty or more maternity beds, as "medium" in sixty-two with twenty to fifty beds, and seventeen as "small" with less than twenty. Sixty-two per cent of the births took place in the voluntary hospitals, 23 per cent in the proprietary, and 15 per cent in the municipal.

Each hospital was rated on a 0-100 scale on compliance with the recommended changes of Section 110 of the Sanitary Code of the City and the standards recommended by the U. S. Children's Bureau and the American Academy of Pediatrics. Hundreds of items were included having to do with the physical equipment and the medical and nursing care of the maternity and newborn services. In the final score only two of the 104 hospitals had a rating of "excellent" (90-100 on the scale position). Twenty-two with a rating of 75-89 were considered as "very good," and thirty-one with a rating of 50-74 as "average." Thirty-one were rated as "fair" (25-49) while nineteen with a score under 25 were rated as "poor" or "very poor." Seventy per cent of the municipal and voluntary hospitals fell into the average or better groups, with the municipal group rating slightly below the voluntary. Less than one-fourth of the proprietary hospitals received an "average or better" score.

As the pediatrician is chiefly interested in the newborn phase of the study, the maternity aspects will be passed over. Less than one-sixth of the hospitals met the standards recommended for delivery units.

So far as the newborn nurseries are concerned only 28 per cent of the hospitals met the recommended standard of 20 square feet per bassinet, and only 15 per cent of not more than 8 bassinets per room in the

nursery unit. In over half of the nurseries the number of cribs was excessive for the size of the nursery, and about one-third failed to meet the requirement of 6 inches or more between bassinets. Twenty-five per cent of the hospitals lacked an incubator or heated crib, and in 36 per cent the oxygen equipment was inadequate. As might be expected there was a definite shortage in the nursing personnel which was more marked in the hospitals with small services. Only half of the hospitals provided proper space for examining rooms for the use of the pediatrician.

It was noted that only forty-four of the 104 hospitals held to the 5.5 pound definition of "premature" adopted by the Children's Bureau and Academy of Pediatrics. In the other hospitals the standard used varied from 4 to 6 pounds. These are but a few of the many interesting findings in the report of the study. At the time it was made less than 25 per cent of the newborn infants in the hospitals were on the breast with the best showing made by the group of municipal hospitals. Only one hospital had a special "rooming-in" service. Eighty per cent of the newborn nurseries were under the charge of a "qualified" pediatrician.

There were many variations found in the maternity and neonatal death rates in different sections of the city which are of more local interest in pointing out areas where future efforts should be centered. In fact, these local differences in some instances are as great as the differences between urban and rural areas. The report is illustrated by numerous graphs and maps, and it is obvious that a thorough objective study has been made after excellent planning and preparation.

B. S. V.

**Functional Endocrinology From Birth Through Adolescence.** Nathan B. Talbot, M.D., Edna H. Sobel, M.D., Janet W. McArthur, M.D., and John D. Crawford, M.D., Cambridge, Mass., 1952, Harvard University Press, 638 pages.

This is a thoughtfully planned and carefully executed text prepared for all physicians "who seek practical information concerning (a) the actions of the endocrine systems in health and ordinary disease and (b) the management of endocrinopathies as they occur in young people."

The volume is complete in its scope, and yet it is written in a concise style which has enabled the authors to include all of the pertinent facts of present-day thinking on this important subject in a single test. Individual sections are devoted to The Thyroid, The Parathyroids, The Adrenal Cortices, The Adrenal Medullae, The Ovaries, The Testes, The Anterior Pituitary, The Posterior Pituitary, and The Pancreatic Islets. Each chapter is prefaced by a section on basic physiology, anatomy, experimental background, and methods of evaluating functional status of the gland considered. The discussions are supplemented by numerous unusually clear and helpful diagrams illustrating the text. This material is designed to provide the reader who is comparatively unfamiliar with the subjects under consideration with sufficient and comprehensive knowledge to enable him to work out the differential diagnosis of subsequently presented clinical examples. In this effort the reviewer feels the authors have been eminently successful.

In the section devoted to Clinical Considerations, the authors present first physiologic alterations in endocrine activity associated with nonendocrine disease and then undertake a discussion of conditions representing primary endocrinopathies. An excellent example of these is found in the section on the adrenal cortices. The complicated interrelationships of the normal pituitary-adrenal response to nonendocrine disease (stress) are established, and the physiologic roles of the adrenal cortical hormones are presented. The picture of primary diseases of the adrenal cortex is then considered and contrasted to the normal physiologic responses.

The text is illustrated with selected case studies and charts, drawn largely from the wealth of the authors' unusually broad clinical experience. Particularly useful are their comments concerning the practical value of certain signs and tests and their applicability in pediatric practice.

This is an excellent and useful volume that will prove of inestimable value to all physicians who see children. A complicated and broadly ramifying subject is presented in a most understandable and readable manner with no sacrifice of accuracy or completeness. This presentation obviously represents the product of many years of careful observation and investigation by a group of

unusually competent observers. In addition they have carefully evaluated and interpreted the voluminous literature. An extensive bibliography is provided. This unique volume should be an essential part of every pediatrician's permanent book shelf.

C. W. DAESCHNER.

**Survey of Clinical Pediatrics.** L. B. Slobody, M.D., New York, 1952, McGraw-Hill Book Company, Inc., 471 pages. Price $7.50.

Dr. Slobody has produced a text for students and practitioners which fits in between the small "compendium," which was so popular twenty to thirty years ago, and the large standard pediatric texts. It is not intended to replace the larger texts. Naturally an abridged text such as this has to gloss over many subjects where controversy and differences of opinion exist. The presentation of the material follows the usual plans of texts, beginning with general material as growth and development, infancy, and then turning to the systemic discussion of disease. The author has succeeded in an excellent way in boiling down his material until only a discussion of essentials is left. This for the purposes and scope of the text is adequate. It should find its chief use as a text for medical students, and in fact much of it is based on material used in teaching at the New York Medical College. It is well written and clear in presentation, and the reviewer has found little to differ with in the various discussions.

**Textbook of Orthopedics.** M. Beckett Howorth, M.D., Philadelphia, 1952, W. B. Saunders Co., 1110 pages. Price $16.00.

Dr. Howorth has written his *Textbook of Orthopedics* primarily for students and orthopedic residents. It is encyclopedic in character, and thus summarizes systematically and briefly the important aspects of subjects covered by the definition of orthopedics, namely, "the art and science of the prevention, diagnosis and treatment of diseases and abnormalities of the musculoskeletal system." The author has been helped by many authorities, not only orthopedists, but in other fields such as pediatrics, neurology, and radiology. In addition there is an extensive bibliography following each chapter.

The book is divided into four sections: I. Introduction and Basic Principles of Orthopedic Practice; II. Regional Orthopedics; III. Orthopedic Disorders; IV. Neurology in Relation to Orthopedic Practice. An innovation in a textbook of this kind is a chapter on anatomy and physiology from the orthopedic standpoint, stressing not only structure but also function.

This text can serve the pediatrician as an excellent reference of orthopedic conditions. There is a detailed chapter on posture, both static and dynamic. Of especial interest to the pediatrician is the extensive review of congenital deformities, and also the discussion of poliomyelitis, and metabolic and endocrine diseases.

D. ELLIOTT O'REILLY

**Die zerebrale Angiographie.** H. Krayenbuhl, Professor of Neurosurgery and Director of the Neurosurgical Clinic, University of Zurich, and H. R. Richter, Assistant, Neurosurgical Clinic, University of Zurich, Stuttgart, 1952, Georg Thieme, 217 pages.

This book presents the techniques, principles, and clinical use of cerebral arteriography in the diagnosis of intracranial vascular abnormalities as well as space-occupying lesions. The first portion of the book includes a discussion of the technique, anatomical, physiological, and pathological aspects of cerebral arteriography. In the second half, the authors have compiled an atlas of arteriography from their collection of 1,500 angiograms done at the Neurosurgical Clinic of the University of Zurich. The atlas is quite complete and includes representative cases of practically all of the central nervous system abnormalities that can be demonstrated by this method. The illustrations, although printed as negatives, are otherwise excellent and make the book well worth reading even by those unfamiliar with German. Many of the photographs are accompanied by line drawings with detailed labelling of the anatomical features which greatly enhance the value of the illustrations. The bibliography is adequate and includes the significant references from both the American and European literature. No comparable monograph has been published in English.

This book is well worth reading by neurosurgeons, neurologists, and radiologists, and perhaps would be of interest to the general medical profession as an indication of the potentialities of this diagnostic technique.

W. B. SEAMAN.

# Editor's Column

## TWENTY YEARS OF THE AMERICAN BOARD OF PEDIATRICS

THIS year marks twenty years of the American Board of Pediatrics. It came into being in 1933 as the result of a report recommending its establishment by a committee appointed "to study the question of limitation of practice" at the first meeting of the Academy of Pediatrics in 1931. At that time specialization was in a state of chaos. There were no standards or educational requirements, and all a licensed physician had to do was to announce to the public, "I am a specialist." While many pediatricians and specialists in other fields had undergone thorough training in their specialty, there were many self-termed pediatricians whose training had consisted of only one or more months of a postgraduate course in pediatrics, and who were without training or experience in a children's hospital. It was not a problem unique to pediatrics and medical leaders in every field were concerned with the situation. Some states were considering the licensing of specialists within their state. Some suggested the National Board of Medical Examiners take on the task of examinations for specialists. Ophthalmology and otolaryngology had been concerned with the problem for a number of years and had come up with voluntary certifying boards. These were rather looked upon askance by the men in other specialties as "certification" being some form of self-aggrandizement.

The Committee studied the problems involved for many months. Compulsory examination could only be exercised by the individual states, which would mean forty-odd examining boards with many different standards. Federal control, analogous to that used by some European countries, was studied and rejected as a solution. The NBME wisely refused to enter into the problem as they would have to set up and take the responsibility for examining boards in each specialty. The committee finally came to the conclusion that the best solution was a national board of examiners in pediatrics for voluntary certification, similar to the two boards mentioned above. A committee of obstetricians reached the same conclusion at practically the same time. It was recognized that whether or not voluntary certification by a Board would gain sufficient prestige to improve the situation would depend upon the support it received from the pediatricians, and that this in turn would depend upon the way the Board conducted its work. From the first the Committee looked upon the problem as essentially one of medical education, and that the real object of a Board was to improve the quality of pediatric practice for the benefit of the children of America. It was not a Board for the personal benefit of the pediatrician. Many pediatricians were skeptical and took a position of watchful waiting, and it was not until the Board had been in operation for several years that a rush developed to be certified.

The Committee considered it essential that the Board should not be a

self-perpetuating body, and that its membership be determined by the pediatricians. It therefore proposed that the Board should be appointed by the three national pediatric organizations, and vacancies when they occurred should be replaced by these organizations. The Board, however, was to be incorporated as an organization —to protect its members as individuals from possible libel suits by disgruntled candidates—and was in no way to be responsible to, nor the responsibility of, the three organizations for the conduct of its work. The report was presented therefore not only to the Academy, but also to the American Pediatric Society and to the Section of the A.M.A. at their annual meetings in 1933. All three adopted the report and each appointed three of its members to the Board. Thus the Board was formed.*

Few realize the problems faced by the original Board as there were no precedents or experience to go by. Unending deliberation took place as to the educational and training requirements before an applicant would be permitted to appear before the Board, and as to the scope, content, and method of the examination. After defining certain groups for men already in practice as specialists, which automatically were done away with after a few years, the Board adopted an educational requirement which has proved so satisfactory that it has not been changed over its years of experience: one year of internship, plus two years of pediatric residency, plus two years of pediatric practice or continued training. It has been quite a different story with the examination. Many changes in scope and content have been made and are still being made. The minutes of the Board are filled with discussions of the examination. An early note from the minutes of the first examination held in Cleveland in June, 1934, states that after a report by the chairman of the Examination Committee, "discussion was carried on into the night by all members of the Board." It goes on to state that the meeting finally adjourned to 10 A.M. the following morning, when fourteen candidates in Groups II and III were examined. Incidentally, ten were passed and four failed—a 28 per cent mortality.

As of Oct. 1, 1952, a total of 4,076 have been certified by the Board. Of these, approximately 400 established pediatricians were certified "on record" up to September, 1936. Since then an examination has been required of all candidates.

Conducting the examination places a tremendous task as well as responsibility upon the Board members. A total of well over 5,000 individual oral examinations have been given, each requiring at least four examiners. In addition to the twenty-two who have served on the Board during these twenty years, there have been over twenty "official examiners" who have helped give the examinations.

*The original appointments were:

By the American Pediatric Society: Aldrich, Helmholz, Van Ingen.

By the American Academy of Pediatrics: Stuart, Veeder, Walker.

By the Section on Pediatrics of the A.M.A.: Davison, Gengenbach, Shaw.

At the organization meeting Veeder was elected president and Aldrich secretary-treasurer. Veeder was succeeded by Casparis in 1941, Shaw in 1943, Aldrich in 1945, McKhann in 1947, and Hill in 1951. Aldrich was succeeded by Hill in 1945 and Poncher in 1951. Dr. John McK. Mitchell became Executive-Secretary in 1948.

The present appointments are as follows:

By the American Pediatric Society: Hughes, Johnston, Weech.

By the American Academy of Pediatrics: Hill, Jacobsen, Poncher.

By the Section on Pediatrics of the A.M.A.: Nelson, Parmelee, Platou.

Others than those mentioned above who have served as members of the Board are McCune, McCulloch, and Roberts.

Up until 1945 the number of candidates each year could be taken care of in three or four two-day examinations each year. In the minutes of the annual meeting of 1938 appears the following statement in the president's report which in the light of subsequent developments is rather amusing.

> As there are slightly over 300 approved residencies in pediatrics and a two-year residency will become an absolute condition in a few years, it does not appear likely that after a few years more than 150 candidates will appear yearly.

No one in the thirties could foresee the impetus that would take place in specialization following a World War II in the early forties. By 1947 the number of pediatric residencies had increased to approximately 700 and by 1949 to 1,000. This impetus is now felt by the Board. It was necessary to hold six examinations in 1951 and in 1952 to accommodate the candidates. Some have been extended to three instead of the usual two or two and one-half days. Thus, so far as examinations are concerned, the Board now has to do in two years what would have been extended over five or six in its earlier years. In 1952 it will require around eighteen days of examinations for teams of ten examiners to take care of the 512 candidates who will be examined. When to this travel time is added, the sacrifice in time alone which members and official examiners give to the work of the Board without remuneration becomes obvious. To this must be added the work of preparing examinations, inspection of residencies, and the passing on qualification of candidates.

The specialty boards, including the Pediatric Board, have made mistakes, as they are organizations made up of human beings, and there have been some unexpected by-products of certification which could not be foreseen twenty years ago. When the picture is looked upon as a whole the American Board of Pediatrics has justified its formation and existence. It has led to infinitely better training of pediatricians, and has markedly improved the quality of work on the pediatric services in our hospitals. The result has been better medical care for American children. This was the underlying purpose and hope of those who were responsible for its founding.

## MATERNITY AND NEONATAL HOSPITAL SERVICES IN NEW YORK

ATTENTION is called to a review of the interesting study of the maternity and newborn services of the hospitals in New York City on page 624 of this issue. While the high standards set by those in charge of the study reveal many deficiencies in the care and equipment provided by New York hospitals, we venture that the study reflects the situation in every large city. In fact, we doubt if in most cities the hospital facilities in these particulars would come up to the level of New York, for the simple reason that few have as low maternity, neonatal, and infant mortality rates as New York.

The IMR in New York in 1950 was twenty-five, a decline from fifty-three in 1933. In 1910, about the time Dr. Josephine Baker was appointed director of the first municipal bureau of child health in the United States, the IMR was 114. Neonatal deaths have been reduced from thirty in 1933 to nineteen in 1950, a fall of 37 per cent. The maternal death rate from child-

birth has been more than two-thirds reduced since 1930. Few cities can match this record.

One of the most important findings is the deficiency in the quality and quantity of pediatric supervision in the newborn nurseries. Some nurseries only provided pediatric care in cases of illness. In others, supervision was nominally in the hands of qualified personnel, but scrutiny showed some of the appointments were only "on paper," and the actual supervision was done by "persons lacking proper qualifications." While correction of the physical deficiencies may take a long time and require the raising of considerable sums of money to make the needed changes, this type of deficiency may be met immediately by developing programs to provide adequate medical care and supervision. It is just here that the pediatricians have a challenge, a responsibility, and an opportunity.

Comparatively speaking, New York ranks high, and the Academy of Medicine and the maternity and child health specialists who outlined and made the study are to be congratulated for their effort to improve their hospital standards and facilities by pointing out the present-day deficiencies. It should stimulate better facilities and better medical care in every community.